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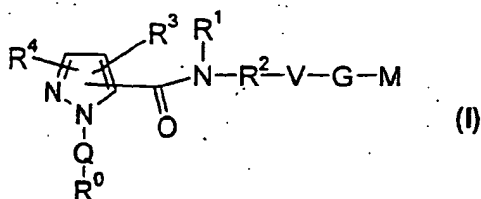
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(54) **Pyrazole-derivatives as factor Xa inhibitors**

(57) The present invention relates to compounds of the formula I,



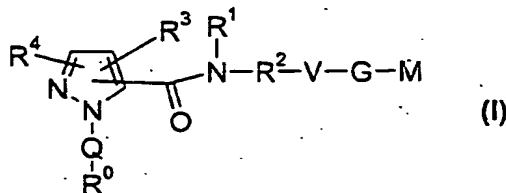
in which R<sup>0</sup>; R<sup>1</sup>; R<sup>2</sup>; R<sup>3</sup>; R<sup>4</sup>; Q; V; G and M have the meanings indicated in the claims. The compounds of the formula I are valuable pharmacologically active com-

pounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa (FXa) and/or factor VIIa (FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

**EP 1 433 788 A1**

## Description

[0001] The present invention relates to compounds of the formula I,



in which  $R^0$ ;  $R^1$ ;  $R^2$ ;  $R^3$ ;  $R^4$ ; Q; V, G and M have the meanings indicated below. The compounds of the formula I are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzymes factor Xa (FXa) and/or factor VIIa (FVIIa), and can in general be applied in conditions in which an undesired activity of factor Xa and/or factor VIIa is present or for the cure or prevention of which an inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

[0002] Normal haemostasis is the result of a complex balance between the processes of clot initiation, formation and clot dissolution. The complex interactions between blood cells, specific plasma proteins and the vascular surface, maintain the fluidity of blood unless injury and blood loss occurs (EP-A-987274). Many significant disease states are related to abnormal haemostasis. For example, local thrombus formation due to rupture of atherosclerotic plaque is a major cause of acute myocardial infarction and unstable angina. Treatment of an occlusive coronary thrombus by either thrombolytic therapy or percutaneous angioplasty may be accompanied by acute thrombolytic reclosure of the affected vessel.

[0003] There continues to be a need for safe and effective therapeutic anticoagulants to limit or prevent thrombus formation. It is most desirable to develop agents that inhibit coagulation without directly inhibiting thrombin but by inhibiting other steps in the coagulation cascade like factor Xa and/or factor VIIa activity. It is now believed that inhibitors of factor Xa carry a lower bleeding risk than thrombin inhibitors (A. E. P. Adang & J. B. M. Rewinkel, *Drugs of the Future* 2000, 25, 369-383).

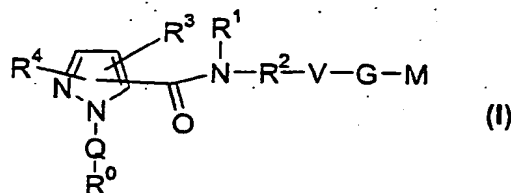
[0004] Low molecular weight, factor Xa-specific blood clotting inhibitors that are effective but do not cause unwanted side effects have been described, for example, in WO-A-95/29189.

However, besides being an effective factor Xa-specific blood clotting inhibitor, it is desirable that such inhibitors also have further advantageous properties, for instance stability in plasma and liver and selectivity versus other serine proteases whose inhibition is not intended, such as thrombin. There is an ongoing need for further low molecular weight factor Xa specific blood clotting inhibitors, which are effective and have the above advantages as well.

[0005] Specific inhibition of the factor VIIa/tissue factor catalytic complex using monoclonal antibodies (WO-A-92/06711) or a protein such as chloromethyl ketone inactivated factor VIIa (WO-A-96/12800, WO-A-97/47651) is an extremely effective means of controlling thrombus formation caused by acute arterial injury or the thrombotic complications related to bacterial septicemia. There is also experimental evidence suggesting that inhibition of factor VIIa/tissue factor activity inhibits restenosis following balloon angioplasty. Bleeding studies have been conducted in baboons and indicate that inhibition of the factor VIIa/tissue factor complex has the widest safety window with respect to therapeutic effectiveness and bleeding risk of any anticoagulant approach tested including thrombin, platelet and factor Xa inhibition. Certain inhibitors of factor VIIa have already been described. EP-A-987274, for example discloses compounds containing a tripeptide unit, which inhibit factor VIIa. However, the property profile of these compounds is still not ideal, and there is an ongoing need for further low molecular weight factor VIIa inhibitory blood clotting inhibitors.

[0006] The present invention satisfies the above needs by providing novel compounds of the formula I, which exhibit better factor Xa and/or factor VIIa inhibitory activity and are favorable agents with high bioavailability.

[0007] Thus, the present invention relates to compounds of the formula I,



wherein

R<sup>0</sup> is

- 1) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R<sub>8</sub>,
- 2) a monocyclic or bicyclic 4- to 15-membered heteroaryl out of the group pyridyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl, benzothiazolyl, benzothiophen, quinazolinyl and phenylpyridyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sub>8</sub>, or
- 3) a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sub>8</sub>, and which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sub>8</sub>,

R<sub>8</sub> is

- 1) halogen,
- 2) -NO<sub>2</sub>,
- 3) -CN,
- 4) -C(O)-NH<sub>2</sub>,
- 5) -OH,
- 6) -NH<sub>2</sub>,
- 7) -O-CF<sub>3</sub>
- 8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or -O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl,
- 9) -(C<sub>1</sub>-C<sub>6</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH<sub>2</sub>, -OH or a methoxy residue, or
- 10) -O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH<sub>2</sub>, -OH or a methoxy residue,
- 11) -SO<sub>2</sub>-CH<sub>3</sub> or
- 12) -SO<sub>2</sub>-CF<sub>3</sub>,

provided that R<sub>8</sub> is at least one halogen, -C(O)-NH<sub>2</sub> or -O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl residue, if R<sup>0</sup> is a monocyclic or bicyclic 6- to 14-membered aryl,

Q

is a direct bond, -(C<sub>0</sub>-C<sub>2</sub>)-alkylene-C(O)-NR<sup>10</sup>-, -NR<sup>10</sup>-C(O)-NR<sup>10</sup>-, -NR<sup>10</sup>-C(O)-, -SO<sub>2</sub>-, -(C<sub>1</sub>-C<sub>6</sub>)-alkylene, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-C(O)-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-S-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-C(O)-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-SO<sub>2</sub>-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-SO<sub>2</sub>-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-CH(OH)-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-O-C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(C<sub>2</sub>-C<sub>3</sub>)-alkylene-O-(C<sub>0</sub>-C<sub>3</sub>)-alkylene-, -(C<sub>2</sub>-C<sub>3</sub>)-alkylene-S(O)-, -(C<sub>2</sub>-C<sub>3</sub>)-alkylene-S(O)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-C(O)-O-(CH<sub>2</sub>)<sub>n</sub>-, -(C<sub>2</sub>-C<sub>3</sub>)-alkylene-S(O)<sub>2</sub>-NH-(R<sup>10</sup>)-, -(C<sub>2</sub>-C<sub>3</sub>)-alkylene-N(R<sup>10</sup>)- or -(C<sub>0</sub>-C<sub>3</sub>)-alkylene-C(O)-O-

wherein R<sup>10</sup> is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by -(CH<sub>2</sub>)<sub>m</sub>- or -(CH<sub>2</sub>)<sub>n</sub>- are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH<sub>2</sub> or -OH; or -C<sub>3</sub>-C<sub>6</sub>- cycloalkylene, wherein cycloalkylene is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH<sub>2</sub> or -OH; a hydrogen atom, -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted, or substituted one to three times by R<sub>13</sub>; -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-C(O)-NH-R<sup>0</sup>, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-C(O)-O-R<sup>15</sup>, a monocyclic or bicyclic

R<sup>1</sup> is

6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above; a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen;  $-(C_1-C_3)$ -perfluoroalkylene,  $-(C_1-C_3)$ -alkylene-S(O)-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,  $-(C_1-C_3)$ -alkylene-S(O)<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub>)-alkyl,  $-(C_1-C_3)$ -alkylene-S(O)<sub>2</sub>-N(R<sup>4</sup>)-R<sup>5</sup>,  $-(C_1-C_3)$ -alkylene-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,  $-(C_0-C_3)$ -alkylene-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, or  $-(C_0-C_3)$ -alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, whereas R14 is defined below,

R<sup>4</sup> and R<sup>5</sup> are independent of one another are identical or different and are hydrogen atom or  $-(C_1-C_4)$ -alkyl,

R<sup>2</sup> is a direct bond or  $-(C_1-C_4)$ -alkylene, or

R<sup>1</sup> and R<sup>3</sup> together with the atoms to which they are bonded form a 4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or form a 4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is halogen, -OH, =O,  $-(C_1-C_6)$ -alkyl,  $-(C_1-C_4)$ -alkoxy, -NO<sub>2</sub>, -C(O)-OH, -CN, -NH<sub>2</sub>, -C(O)-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,  $-(C_1-C_6)$ -alkylsulfonyl, -SO<sub>2</sub>, -C(O)-NH-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, -C(O)-N-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]<sub>2</sub>, -NR<sup>18</sup>.C(O)-NH-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, -C(O)-NH<sub>2</sub>, -S-R<sup>18</sup>, or -NR<sup>18</sup>.C(O)-NH-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]<sub>2</sub>, wherein R<sup>18</sup> is hydrogen atom,  $-(C_1-C_3)$ -perfluoroalkyl or  $-(C_1-C_6)$ -alkyl,

V is

- 1) a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,
- 2) a 6- to 14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, or
- 3) a monocyclic or bicyclic 4- to 15-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is

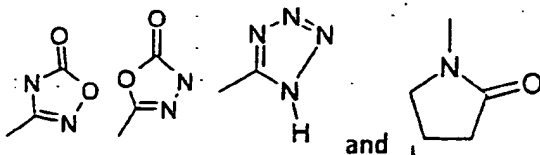
a direct bond,  $-(CH_2)_m$ -NR<sup>10</sup>-SO<sub>2</sub>-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>,  $-(CH_2)_m$ -CH(OH)-(CH<sub>2</sub>)<sub>n</sub>,  $-(CH_2)_m$ ,  $-(CH_2)_m$ -O-(CH<sub>2</sub>)<sub>n</sub>,  $-(CH_2)_m$ -C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>,  $-(CH_2)$ -SO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>,  $-(CH_2)_m$ -NR<sup>10</sup>-C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>,  $-(CH_2)_m$ -NR<sup>10</sup>-C(O)-(CH<sub>2</sub>)<sub>n</sub>,  $-(CH_2)_m$ -C(O)-(CH<sub>2</sub>)<sub>n</sub>,  $-(CH_2)$ -S-(CH<sub>2</sub>)<sub>n</sub>,  $-(CH_2)_m$ -SO<sub>2</sub>-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>,  $-(CH_2)_m$ -NR<sup>10</sup>-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>,  $-(CH_2)_m$ -NR<sup>10</sup>,  $-(CH_2)_m$ -O-C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub> or  $-(CH_2)_m$ -NR<sup>10</sup>-C(O)-O-(CH<sub>2</sub>)<sub>n</sub>,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

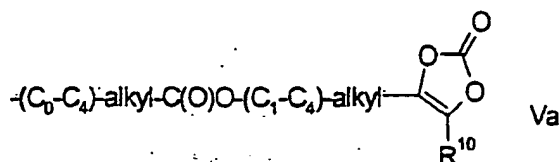
R<sup>10</sup> is hydrogen atom,  $-(C_1-C_3)$ -perfluoroalkyl or  $-(C_1-C_6)$ -alkyl,

M is

- 1) a hydrogen atom,
- 2)  $-(C_1-C_6)$ -alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,
- 3) -C(O)-N(R<sup>11</sup>)-R<sup>12</sup>,
- 4)  $-(CH_2)_m$ -NR<sup>10</sup>,
- 5)  $-(C_6-C_{14})$ -aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,
- 6)  $-(C_4-C_{15})$ -heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,
- 7)  $-(C_3-C_8)$ -cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or
- 8) a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,



or a residue of formula Va,

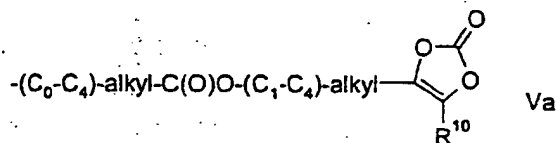


wherein  $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are as defined above and  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are as defined below, independently of one another hydrogen,  $-(C_1-C_6)\text{-alkyl}$ , or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by  $R^{10}$ ,

$R^{17}$  is  $-(C_1-C_6)\text{-alkyl}$ ,  $-(C_3-C_6)\text{-cycloalkyl}$ ,  $-(C_1-C_6)\text{-alkyl-(C}_3\text{-C}_6\text{)-cycloalkyl}$  wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by  $R^{10}$ , and

$R^3$  and  $R^4$  are independent of one another are identical or different and are

- 1) hydrogen atom,
- 2) halogen,
- 3)  $-(C_1-C_4)\text{-alkyl}$ , wherein alkyl is unsubstituted or substituted one to three times by  $R^{13}$ ,
- 4)  $-(C_1-C_3)\text{-perfluoroalkyl}$ ,
- 5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by  $R^{13}$ ,
- 6)  $-(C_1-C_4)\text{-alkyl}$ , wherein alkyl is unsubstituted or substituted one to three times by  $R^{13}$ ,
- 7)  $-\text{NO}_2$ ,
- 8)  $-\text{CN}$ ,
- 9)  $-\text{OH}$ ,
- 10) phenoxy-, wherein phenoxy is unsubstituted or substituted one to three times by  $R^{13}$ ,
- 11) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one to three times by  $R^{13}$ ,
- 12)  $-\text{C(O)-O-R}^{11}$ ,
- 13)  $-(C_0-C_4)\text{-alkylene-C(O)-N(R}^{11}\text{)-R}^{12}$ ,
- 14)  $-\text{N(R}^{11}\text{)-R}^{12}$ ,
- 15)  $-\text{NR}^{10}\text{-SO}_2\text{-R}^{10}$ ,
- 16)  $-\text{S-R}^{10}$ ,
- 17)  $-\text{SO}_s\text{-R}^{10}$ , wherein  $s$  is 1 or 2,
- 18)  $-\text{SO}_2\text{-N(R}^{11}\text{)-R}^{12}$ ,
- 19)  $-\text{C(O)-R}^{10}$ , wherein  $R^{10}$  is as defined above,
- 20)  $-\text{C(O)-O-C(R}^{15}, \text{R}^{16})\text{-O-C(O)-R}^{17}$ , wherein  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are as defined above,
- 21)  $-\text{C(O)-O-C(R}^{15}, \text{R}^{16})\text{-O-C(O)-O-R}^{17}$ , wherein  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are as defined above,
- 22) a residue of formula Va,



wherein  $R^{10}$  is defined as above,

- 23)  $-\text{NR}^{10}\text{-(C}_1\text{-C}_4\text{)-alkyl}$ , wherein alkyl is unsubstituted or substituted one, two or three times

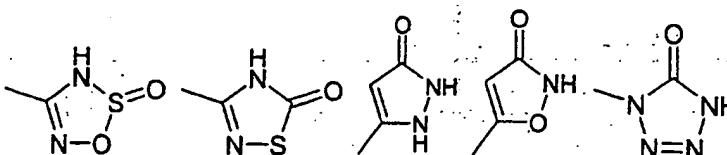
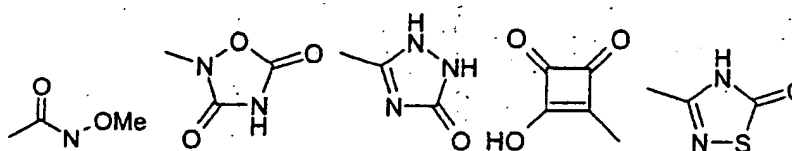
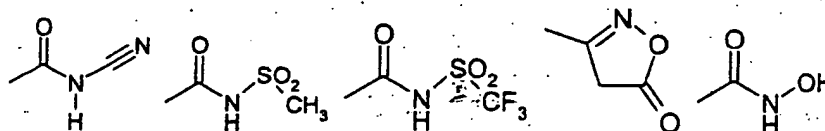
substituted independently of one another by R14, wherein R14 is defined above,

R11 and R12 are independently of one another identical or different and are

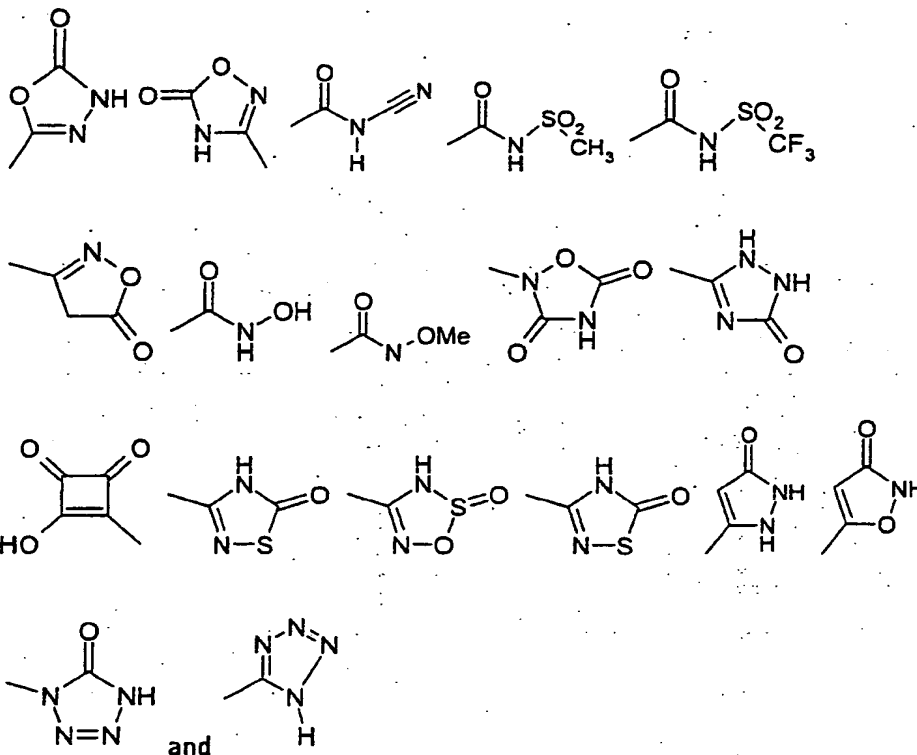
- 1) hydrogen atom,
- 2)  $-(C_1-C_6)$ -alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
- 3)  $-(C_3-C_8)$ -cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
- 4)  $-(C_1-C_4)$ -alkyl- $-(C_6-C_{14})$ -aryl, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,
- 5)  $-(C_6-C_{14})$ -aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
- 6)  $-(C_4-C_{15})$ -heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13 or
- 7)  $-(C_1-C_4)$ -alkyl- $-(C_4-C_{15})$ -heteroaryl, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

R11 and R12 together with the nitrogen atom to which they are bonded form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

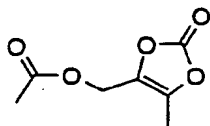
R13 is halogen,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-(C_0-C_6)$ -alkyl-OH,  $-(C_1-C_8)$ -alkyl,  $-(C_1-C_8)$ -alkoxy,  $-(C_0-C_6)$ -alkyl- $CF_3$ , phenyl, phenyloxy-,  $-(C_0-C_6)$ -alkyl-C(O)-O-R<sup>11</sup>,  $-(C_3-C_8)$ -cycloalkyl, phenyl- $-(C_1-C_4)$ -alkoxy-,  $-(C_0-C_6)$ -alkyl-C(O)-N(R<sup>11</sup>)-R<sup>12</sup>,  $-(C_0-C_6)$ -alkyl-N(R<sup>11</sup>)-R<sup>12</sup>,  $-NR^{10}$ ,  $-SO_2-R^{10}$ ,  $-S-R^{10}$ ,  $-S(O)_r-R^{10}$ , wherein r is 1 or 2;  $-(C_0-C_6)$ -alkyl-Si(R<sup>10</sup>)<sub>s</sub>, wherein s is 1, 2 or 3,  $-(C_0-C_6)$ -alkyl-S(O)<sub>r</sub>- $-(C_0-C_6)$ -alkyl, wherein r is as defined above,  $-(C_0-C_6)$ -alkyl-S(O)<sub>r</sub>-N(R<sup>11</sup>)-R<sup>12</sup>; wherein r is as defined above,  $-C(O)-R^{10}$ ,  $-(C_0-C_4)$ -alkyl-C(O)-O-C(R<sup>15</sup>, R<sup>16</sup>)-O-C(O)-R<sup>17</sup>,  $-CN$ ,  $-(C_0-C_4)$ -alkyl-C(O)-O-C(R<sup>15</sup>, R<sup>16</sup>)-O-C(O)-O-R<sup>17</sup>,  $-(C_1-C_4)$ -perfluoroalkyl,  $-O-R^{15}$ ,  $-O-CF_3$ ,  $-C(O)-O-R^{15}$ ,  $-C(O)-H$ ,  $-NH-C(O)-NH-R^{10}$ ,  $-NH-C(O)-O-R^{15}$ ,  $-(C_1-C_3)$ -alkylene-O- $-(C_1-C_3)$ -alkyl, or a residue from the following list



- by R13,  
 24)  $-O-CF_3$ ,  
 25) a residue from the following list



- 26)  $-(C_0-C_4)\text{-alkylene-(C}_6\text{-C}_{14}\text{)-aryl}$ , wherein aryl is mono-, di- or trisubstituted independently of one another by R13 and is as defined above,  
 27)  $-(C_0-C_4)\text{-alkylene-(C}_4\text{-C}_{15}\text{)-heteroaryl}$ , wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,  
 28)  $-(C_0-C_2)\text{alkylene-C(O)-O-(C}_1\text{-C}_4\text{)-alkylene-O-C(O)-(C}_1\text{-C}_4\text{)-alkyl}$ ,  
 29)  $-(C_0-C_2)\text{alkylene-C(O)-O-(C}_1\text{-C}_4\text{)-alkylene-O-C(O)-O-(C}_1\text{-C}_7\text{)-alkyl}$ ,  
 30)



- 31)  $-(C_0-C_4)\text{-alkylene-(C}_3\text{-C}_8\text{)-cycloalkyl}$ , wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or  
 32)  $-(C_0-C_4)\text{-alkylene-het}$ , wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

The present invention also relates to the compounds of the formula I, wherein

R<sup>0</sup> is 1. a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisub-

stituted independently of one another by R<sup>8</sup>,

2. a monocyclic or bicyclic 4- to 14-membered heteroaryl out of the group pyridyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl, benzothiazolyl, benzothiophen, quinazolinyl and phenylpyridyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>, or

3. a monocyclic or bicyclic 4- to 14-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>, and which is additionally substituted by a monocyclic or bicyclic 4- to 14-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>,

R<sup>8</sup> is

1. halogen,
2. -NO<sub>2</sub>,
3. -CN,
4. -C(O)-NH<sub>2</sub>,
5. -OH,
6. -NH<sub>2</sub>,
7. -OCF<sub>3</sub>,

8. a monocyclic or bicyclic 4- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or -O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl,

9. -(C<sub>1</sub>-C<sub>8</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH<sub>2</sub>, -OH or a methoxy residue, or

10. -O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH<sub>2</sub>, -OH or a methoxy residue,

11. -SO<sub>2</sub>CH<sub>3</sub> or

12. -SO<sub>2</sub>CF<sub>3</sub>,

provided that R<sup>8</sup> is at least one halogen, -C(O)-NH<sub>2</sub> or -O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl residue, if R<sup>0</sup> is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -(C<sub>0</sub>-C<sub>2</sub>)-alkylene-C(O)-NR<sup>10</sup>-, -NR<sup>10</sup>-C(O)-NR<sup>10</sup>-, -NR<sup>10</sup>-C(O)-, -SO<sub>2</sub>-, -(C<sub>1</sub>-C<sub>6</sub>)-alkylene,

R<sup>1</sup> is a hydrogen atom, -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>; -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-C(O)-NH-R<sup>0</sup>, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-C(O)-O-R<sup>15</sup>, -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkylene, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-S(O)-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-S(O)<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub>)-alkyl, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-S(O)<sub>2</sub>-N(R<sup>4'</sup>)-R<sup>5'</sup>, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>0</sub>-C<sub>3</sub>)-alkylene-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, or -(C<sub>0</sub>-C<sub>3</sub>)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen,

wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, whereas R<sup>14</sup> is defined below,

R<sup>4'</sup> and R<sup>5'</sup> are independent of one another are identical or different and are hydrogen atom or -(C<sub>1</sub>-C<sub>4</sub>)-alkyl,

R<sup>2</sup> is a covalent bond or -(C<sub>1</sub>-C<sub>4</sub>)-alkylene, or

R<sup>1</sup> and R<sup>3</sup> together with the atoms to which they are bonded can form a 4- to 7-membered cyclic group, containing up to 1 or 2 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

R<sup>1</sup>-N-R<sup>2</sup>-V can form a 4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

R<sup>14</sup> is halogen, -OH, =O, -(C<sub>1</sub>-C<sub>8</sub>)-alkyl, -(C<sub>1</sub>-C<sub>4</sub>)-alkoxy, -C(O)-OH, -CN, -NH<sub>2</sub>, -C(O)-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>1</sub>-C<sub>8</sub>)-alkylsulfonyl, -C(O)-NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, -C(O)-N-[(C<sub>1</sub>-C<sub>8</sub>)-



alkyl]<sub>2</sub>, -NR<sup>10</sup>-C(O)-NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, -C(O)-NH<sub>2</sub>, -NR<sup>10</sup>-C(O)-NH-[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>,  
wherein R<sup>10</sup> is hydrogen atom, -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkyl or -(C<sub>1</sub>-C<sub>6</sub>)-alkyl,

V is

1. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

2. a 6- to 14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, or

3. a monocyclic or bicyclic 4- to 14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

G is

a covalent bond, -(CH<sub>2</sub>)<sub>m</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-,  
-(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-C(O)-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-SO<sub>2</sub>-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-  
NR<sup>10</sup>-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-, -(CH<sub>2</sub>)<sub>m</sub>-O-C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>- or -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-C(O)-  
-O-(CH<sub>2</sub>)<sub>n</sub>-.

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

R<sup>10</sup> is hydrogen atom, -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkyl or -(C<sub>1</sub>-C<sub>6</sub>)-alkyl,

M is

1. a hydrogen atom,

2. -(C<sub>1</sub>-C<sub>8</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

3. -C(O)-NR<sup>11</sup>R<sup>12</sup>,

4. -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>,

5. -(C<sub>6</sub>-C<sub>14</sub>)-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

6. -(C<sub>4</sub>-C<sub>14</sub>)-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

7. (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, or

8. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, wherein R<sup>14</sup> is defined above,

R<sup>11</sup> and R<sup>12</sup>

are independently of one another identical or different and are

1) hydrogen atom,

2) -(C<sub>1</sub>-C<sub>6</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,

3) -(C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,

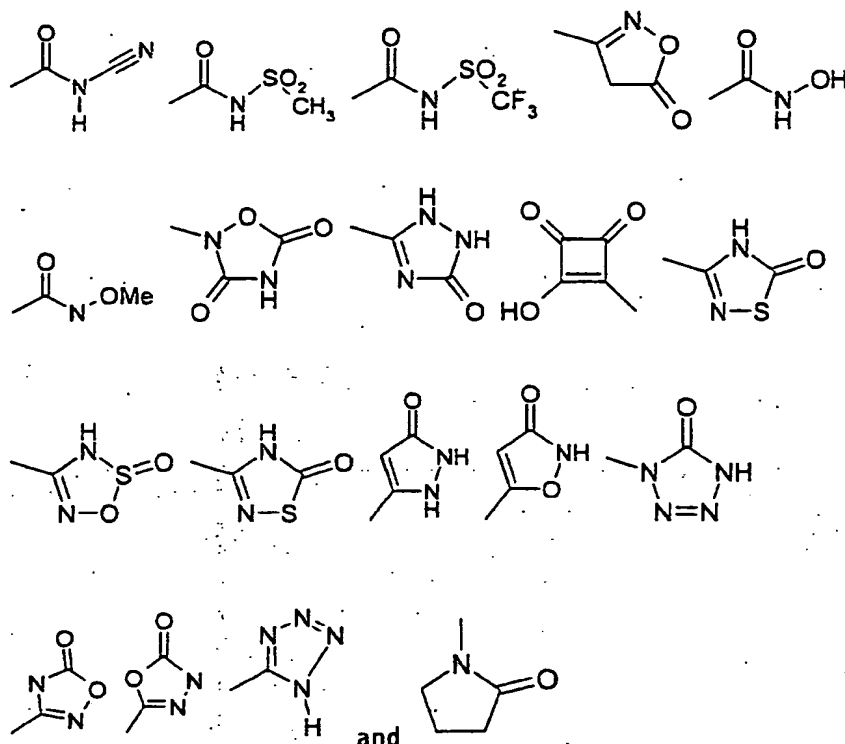
4) -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-(C<sub>4</sub>-C<sub>15</sub>)-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>, or

R<sup>11</sup> and R<sup>12</sup>

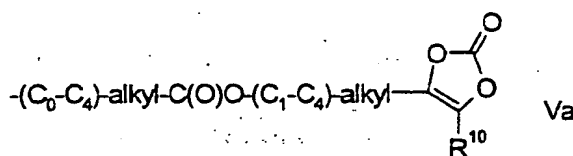
together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,

R<sup>13</sup> is

halogen, -NO<sub>2</sub>, -CN, =O, -(C<sub>0</sub>-C<sub>6</sub>)-alkyl-OH, -(C<sub>1</sub>-C<sub>8</sub>)-alkyl, -(C<sub>1</sub>-C<sub>8</sub>)-alkoxy, -(C<sub>0</sub>-C<sub>6</sub>)-alkyl-CF<sub>3</sub>,  
phenyl, phenyloxy-, -(C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)-O-R<sup>11</sup>, -(C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, phenyl-(C<sub>1</sub>-C<sub>4</sub>)-alkoxy-,  
-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)-N(R<sup>11</sup>)-R<sup>12</sup>, -(C<sub>0</sub>-C<sub>6</sub>)-alkyl-N(R<sup>11</sup>)-R<sup>12</sup>, -NR<sup>10</sup>-SO<sub>2</sub>-R<sup>10</sup>, -S-R<sup>10</sup>, -S(O)-R<sup>10</sup>,  
wherein r is 1 or 2; -(C<sub>0</sub>-C<sub>6</sub>)-alkyl-Si-(R<sup>10</sup>)<sub>s</sub>, wherein s is 1, 2 or 3, -(C<sub>0</sub>-C<sub>6</sub>)-alkyl-S(O)-R<sup>10</sup>,  
alkyl, wherein r is as defined above, -(C<sub>0</sub>-C<sub>6</sub>)-alkyl-S(O)-N(R<sup>11</sup>)-R<sup>12</sup>, wherein r is as defined  
above, -C(O)-R<sup>10</sup>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-C(O)-O-C(R<sup>15</sup>, R<sup>16</sup>)-O-C(O)-R<sup>17</sup>, -CN, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-C(O)-  
-O-C(R<sup>15</sup>, R<sup>16</sup>)-O-C(O)-O-R<sup>17</sup>, -(C<sub>1</sub>-C<sub>4</sub>)-perfluoroalkyl, -O-R<sup>15</sup>, -O-CF<sub>3</sub>, -C(O)-O-R<sup>15</sup>, -C(O)-H,  
-NH-C(O)-NH-R<sup>10</sup>, -NH-C(O)-O-R<sup>15</sup>, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-O-(C<sub>1</sub>-C<sub>3</sub>)-alkyl, or a residue from the following list



or a residue of formula Va,



wherein  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$  are as defined above and  $R^{15}$ ,  $R^{16}$  or  $R^{17}$  are as defined below,

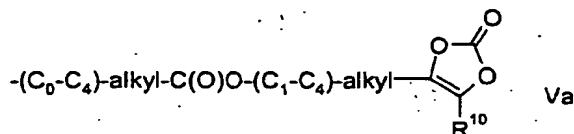
$R^{15}$  and  $R^{16}$  are independently of one another hydrogen,  $-(C_1-C_6)$ -alkyl, or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by  $R^{10}$ ,

$R^{17}$  is  $-(C_1-C_6)$ -alkyl,  $-(C_1-C_6)$ -cycloalkyl,  $-(C_1-C_6)$ -alkyl- $-(C_1-C_6)$ -cycloalkyl wherein said cycloalkyl ring is unsubstituted or substituted one to three times by  $R^{10}$ , and

$R^3$  and  $R^4$  are independent of one another are identical or different and are

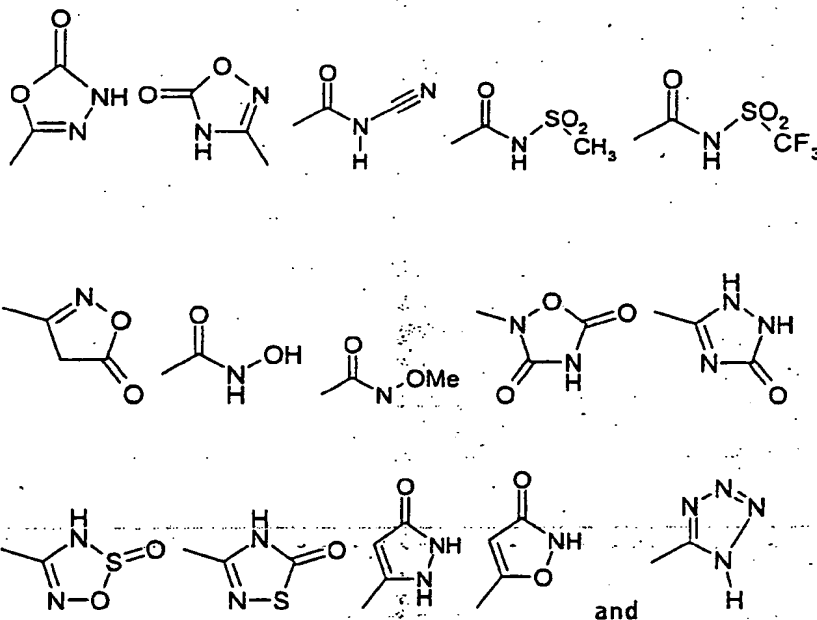
- 1) hydrogen atom,
- 2) halogen,
- 3)  $-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or substituted one to three times by  $R^{13}$ ,
- 4)  $-(C_1-C_3)$ -perfluoroalkyl,
- 5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by  $R^{13}$ ,
- 6)  $-O-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or substituted one to three times by  $R^{13}$ ,

- 7) -CN,  
 8) -OH,  
 9) phenoxy-, wherein phenoxy is unsubstituted or substituted one to three times by R<sup>13</sup>,  
 10) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one to three times by R<sup>13</sup>,  
 11) -C(O)-O-R<sup>11</sup>,  
 12) -(C<sub>0</sub>-C<sub>4</sub>)alkyl-C(O)-N-R<sup>11</sup>R<sup>12</sup>,  
 13) -NR<sup>11</sup>R<sup>12</sup>,  
 14) -NR<sup>10</sup>-SO<sub>2</sub>-R<sup>10</sup>,  
 15) -SO<sub>n</sub>-R<sup>10</sup>, wherein n is 1 or 2,  
 16) -SO<sub>2</sub>-NR<sup>11</sup>R<sup>12</sup>,  
 17) -C(O)-O-C(R<sup>15</sup>R<sup>16</sup>)-O-C(O)-R<sup>17</sup>, wherein R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined above,  
 18) -C(O)-O-C(R<sup>15</sup>R<sup>16</sup>)-O-C(O)-R<sup>17</sup>, wherein R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined above,  
 19) residue of formula Va,



wherein R<sup>10</sup> is defined as above,

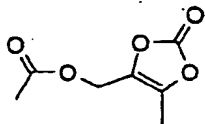
- 20) -NR<sup>10</sup>-(C<sub>1</sub>-C<sub>4</sub>)alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,  
 21) -OCF<sub>3</sub>,  
 22) a residue from the following list



- 23) -(C<sub>0</sub>-C<sub>2</sub>)-alkylene-aryl, wherein aryl is a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R<sup>13</sup>, wherein R<sup>13</sup> is as defined above,  
 24) -(C<sub>0</sub>-C<sub>2</sub>)-alkylene-heteroaryl, wherein heteroaryl is a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one

another by R<sup>13</sup>,

- 25)  $-(C_0-C_2)\text{alkyl}-C(O)-O-(C_1-C_4)\text{-alkyl}-O-C(O)-(C_1-C_4)\text{-alkyl}$ ,  
 26)  $-(C_0-C_2)\text{alkyl}-C(O)-O-(C_1-C_4)\text{-alkyl}-O-C(O)O-(C_1-C_7)\text{-alkyl}$ ,  
 27)



- 28)  $-(C_0-C_2)\text{-alkylene-(C}_3\text{-C}_8\text{)-cycloalkyl}$ ,  $-(C_0-C_3)\text{-alkylene-het}$ , wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,  
 29)  $-(C_0-C_2)\text{-alkylene-het}$ , wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>, wherein R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined above,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

3) The present invention also relates to the compounds of the formula I, wherein

R<sup>0</sup> is 1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>,

25 2. a bicyclic 5- to 14-membered heteroaryl selected out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, chromanyl, cinnolyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolyl, phthalazinyl, pteridyl, purinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyridyl, quinazolyl, quinolyl and quinoxalyl,

30 wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>,

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyridazinyl, thiophenyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>

35 3. a monocyclic 5- to 14-membered heteroaryl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl,

40 wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>,

45 and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl, thiophenyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>

R<sup>8</sup> is 1. F, Cl, Br or I,

2.  $-C(O)-NH_2$ ,

50 3.  $-(C_1-C_4)\text{-alkyl}$ , wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or

4.  $-O-(C_1-C_4)\text{-alkyl}$ , wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that R<sup>8</sup> is at least one halogen,  $-C(O)-NH_2$  or  $-O-(C_1-C_8)\text{-alkyl}$  residue, if R<sup>0</sup> is phenyl, is a direct bond,  $-C(O)-$ ,  $-SO_2-$  or  $-(C_1-C_6)\text{-alkylene}$ ,  $-(C_0-C_2)\text{-alkylene}-C(O)-NR^{10}$ ,

55 hydrogen atom or  $-(C_1-C_2)\text{-alkyl}$ ,  $-(C_1-C_3)\text{-alkylene}-C(O)-NH-R^0$ ,  $-(C_1-C_3)\text{-alkylene}-C(O)-O-R^{15}$ ,  $-(C_1-C_3)\text{-perfluoroalkylene}$ ,  $-(C_1-C_3)\text{-alkylene}-S(O)_2-(C_1-C_3)\text{-alkyl}$  or  $-(C_1-C_3)\text{-alkylene}-S(O)_2-N(R^4)-R^5$ ,

R<sup>2</sup> is a direct bond or  $-(C_1-C_2)\text{-alkylene}$ , or

R<sup>1</sup>-N-R<sup>2</sup>-V

can form a 4- to 7- membered cyclic group out of the group azetidine, azetidinone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

R<sup>14</sup> is halogen, -OH, =O, -(C<sub>1</sub>-C<sub>8</sub>)-alkyl, -C(O)-OH, -CN, -NH<sub>2</sub>,  
-C(O)-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>1</sub>-C<sub>8</sub>)-alkylsulfonyl, -C(O)=NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl,  
-C(O)-N-[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, -C(O)-NH<sub>2</sub>, -NR<sup>10</sup> wherein R<sup>10</sup> is hydrogen atom, -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkyl or -(C<sub>1</sub>-C<sub>6</sub>)-alkyl,

V is

1. a 3- to 7-membered cyclic residue out of the group containing compounds which are derived from aziridine, azirine, azetidine, azetidinone, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine,

wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, or

3. a bicyclic 5- to 14-membered heteroaryl out of the group quinolyl, isoquinolyl and quinoxaliny, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

G is

a direct bond, -(CH<sub>2</sub>)<sub>m</sub>-, or -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>,

m is the integers zero, 1, 2, 3 or 4,

R<sup>10</sup> is hydrogen atom, -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkyl or -(C<sub>1</sub>-C<sub>4</sub>)-alkyl,

M is

1. a hydrogen atom,

2. -(C<sub>6</sub>-C<sub>14</sub>)-heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, thiadiazole or thiomorpholine, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

3. -(C<sub>1</sub>-C<sub>6</sub>)-alkyl, wherein alkyl is unsubstituted, or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, or

4. (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl,

R<sup>11</sup> and R<sup>12</sup> are

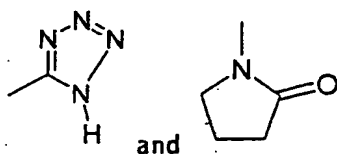
independently of one another identical or different and are

- 1) hydrogen atom,
- 2) -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,
- 3) -(C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,
- 4) -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-(C<sub>4</sub>-C<sub>15</sub>)-heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from azaspirodecane, azetidine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, dihydrooxazol, imidazole, imidazolidine, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazepane, oxazole, oxazolidine, piperazine, piperidine, pyrazine, pyrazole, pyridazine, pyridine, pyridonyl, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, tetrazine, tetrazole, thiadiazole, thiazole, thiazolidine, thiomorpholine, thiophenyl, 1,2,3-tri-

azine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,

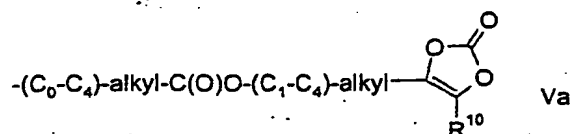
R<sup>11</sup> and R<sup>12</sup> together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring, wherein said heterocyclic ring is a residue out of the group which can be derived from azaspirodecan, azetidine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, dihydrooxazol, imidazole, imidazolidine, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazepane, oxazole, oxazolidine, piperazine, piperidine, pyrazine, pyrazole, pyridazine, pyridine, pyridonyl, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydro-pyran, tetrazine, tetrazole, thiadiazole, thiazole, thiazolidine, thiomorpholine, thiophenyl, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,

R<sup>13</sup> is Cl, -CN, =O, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-OH, -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>1</sub>-C<sub>4</sub>)-alkoxy, -(C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-CF<sub>3</sub>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-C(O)-O-R<sup>11</sup>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-C(O)-N(R<sup>11</sup>)-R<sup>12</sup>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-N(R<sup>11</sup>)-R<sup>12</sup>, -S(O)<sub>2</sub>-CH<sub>3</sub>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-Si-(CH<sub>3</sub>)<sub>3</sub>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-S(O)<sub>r</sub>-(C<sub>0</sub>-C<sub>4</sub>)-alkyl, wherein r is 2, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-S(O)<sub>r</sub>-N(R<sup>11</sup>)-R<sup>12</sup>, wherein r is 2, -(C<sub>1</sub>-C<sub>2</sub>)-alkylene-O-(C<sub>1</sub>-C<sub>2</sub>)-alkyl or a residue from the following list



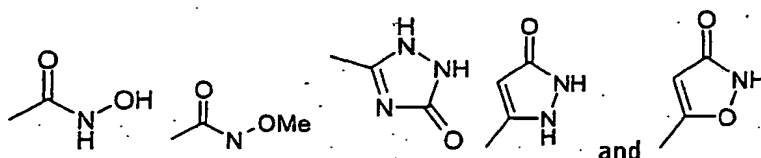
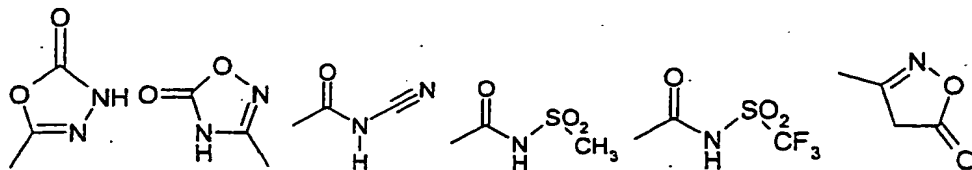
R<sup>15</sup>, R<sup>16</sup> or R<sup>17</sup> are independently of one another hydrogen or -(C<sub>1</sub>-C<sub>6</sub>)-alkyl, R<sup>3</sup> and R<sup>4</sup>, are independent of one another are identical or different and are

- 1) hydrogen atom,
- 2) halogen,
- 3) -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,
- 4) -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkyl,
- 5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R<sup>13</sup>,
- 6) -O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,
- 7) -CN,
- 8) -OH,
- 9) phenyloxy-, wherein phenyloxy is unsubstituted or substituted one to three times by R<sup>13</sup>,
- 10) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one to three times by R<sup>13</sup>,
- 11) -C(O)-O-R<sup>11</sup>,
- 12) -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-C(O)-N-R<sup>11</sup>R<sup>12</sup>,
- 13) -NR<sup>11</sup>R<sup>12</sup>,
- 14) -NR<sup>10</sup>-SO<sub>2</sub>-R<sup>10</sup>,
- 15) -SO<sub>n</sub>-R<sup>10</sup>, wherein n is 1 or 2,
- 16) -SO<sub>2</sub>-NR<sup>11</sup>R<sup>12</sup>,
- 17) -C(O)-O-C(R<sup>15</sup>R<sup>16</sup>)-O-C(O)-R<sup>17</sup>, wherein R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined above,
- 18) -C(O)-O-C(R<sup>15</sup>R<sup>16</sup>)-O-C(O)-R<sup>17</sup>, wherein R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined above,
- 19) residue of formula Va,

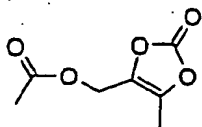


wherein R<sup>10</sup> is defined as above,

- 20) -NR<sup>10</sup>-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,  
21) -OCF<sub>3</sub>, or  
22) a residue from the following list



- 23)  $-(C_0-C_2)\text{-alkyl-C(O)-O-(C}_1\text{-C}_4\text{)-alkyl-O-C(O)-(C}_1\text{-C}_4\text{)-alkyl,}$   
 24)  $-(C_0-C_2)\text{-alkylene-C(O)-O-(C}_1\text{-C}_4\text{)-alkylene-O-C(O)-O-(C}_1\text{-C}_7\text{)-alkyl or}$   
 25)



wherein R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>15</sup>, R<sup>16</sup> or R<sup>17</sup> are as defined above.

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

4)  $R^0$  is

The present invention also relates to the compounds of the formula I, wherein

1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>9</sup>.

2. a bicyclic 5- to 14-membered heteroaryl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolnlyl, isoquinolnlyl, chromanyl, isochromanyl, cinnolnlyl, quinazolnlyl, quinoxalynyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl,

wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>.

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, , triazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, thiophenyl, pyrimidinyl, pyridazinyl and pyrazinyl, wherein said residue is-unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>

3. a monocyclic 5- to 14-membered heteroaryl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>.

and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiophenyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>B</sup>

R<sup>8</sup> is

1. halogen, such as F, Cl, Br or J,
  2. -C(O)-NH<sub>2</sub>,
  3. -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -OH or a methoxy residue, or
  4. -O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,
- provided that R<sup>8</sup> is at least one halogen, -C(O)-NH<sub>2</sub> or -O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl residue, if R<sup>9</sup> is a mono-cyclic or bicyclic 6- to 14-membered aryl,

Q

R<sup>1</sup> isR<sup>2</sup> isR<sup>1</sup>-N-R<sup>2</sup>-V

- is a direct bond, -C(O)-; -SO<sub>2</sub>- or -(C<sub>1</sub>-C<sub>6</sub>)-alkylen, -(C<sub>0</sub>-C<sub>2</sub>)-alkylen-C(O)-NR<sup>10</sup>-, hydrogen atom or -(C<sub>1</sub>-C<sub>2</sub>)-alkyl, a direct bond or -(C<sub>1</sub>-C<sub>2</sub>)-alkylen, or can form a 5- to 7- membered cyclic group out of the group piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

R<sup>14</sup> isR<sup>11</sup> and R<sup>12</sup> are

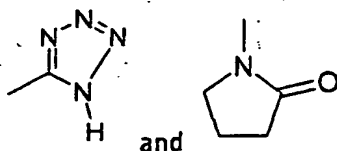
- halogen, -(C<sub>1</sub>-C<sub>4</sub>)-alkyl or -NH<sub>2</sub>, independently of one another identical or different and are

- 1) hydrogen atom,
- 2) -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,
- 3) -(C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,
- 4) -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-(C<sub>4</sub>-C<sub>15</sub>)-heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from azaspirodecan, azetidine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, dihydrooxazol, imidazole, imidazolidine, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazepane, oxazole, oxazolidine, piperazine, piperidine, pyrazine, pyrazole, pyridazine, pyridine, pyridonyl, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, tetrazine, tetrazole, thiadiazole, thiazole, thiazolidine, thiomorpholine, thiophenyl, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,

R<sup>11</sup> and R<sup>12</sup>

together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring, wherein said heterocyclic ring is a residue out of the group which can be derived from azaspirodecan, azetidine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, dihydrooxazol, imidazole, imidazolidine, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazepane, oxazole, oxazolidine, piperazine, piperidine, pyrazine, pyrazole, pyridazine, pyridine, pyridonyl, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, tetrazine, tetrazole, thiadiazole, thiazole, thiazolidine, thiomorpholine, thiophenyl, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>, Cl, -CN, =O, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-OH, -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>1</sub>-C<sub>4</sub>)-alkoxy, -(C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-CF<sub>3</sub>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-C(O)-O-R<sup>11</sup>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-C(O)-N(R<sup>11</sup>)-R<sup>12</sup>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-N(R<sup>11</sup>)-R<sup>12</sup>, -S(O)<sub>2</sub>-CH<sub>3</sub>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-Si-(CH<sub>3</sub>)<sub>3</sub>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-S(O)<sub>r</sub>-(C<sub>0</sub>-C<sub>4</sub>)-alkyl, wherein r is 2, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-S(O)<sub>r</sub>-N(R<sup>11</sup>)-R<sup>12</sup>, wherein r is 2, -(C<sub>1</sub>-C<sub>2</sub>)-alkylene-O-(C<sub>1</sub>-C<sub>2</sub>)-alkyl or a residue from the following list





V is

1. a 3- to 7-membered cyclic residue out of the group containing compounds, which are derived from aziridine, azirine, azetidine, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran; 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine,

wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ ,

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ , or

3. a bicyclic 5- to 14-membered heteroaryl out of the group quinolyl, isoquinolyl and quinoxaliny, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ ,

G is

a direct bond,  $-(CH_2)_m-$ , or  $-(CH_2)_m-NR^{10}$ ,

m is the integers zero, 1, 2, 3 or 4,

$R^{10}$  is hydrogen atom,  $-(C_1-C_3)$ -perfluoroalkyl or  $-(C_1-C_4)$ -alkyl,

M is

1. a hydrogen atom,

2.  $-(C_5-C_{14})$ -heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, thiadiazole or thiomorpholine, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ ,

3.  $-(C_1-C_6)$ -alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ , or

4.  $(C_3-C_6)$ -cycloalkyl,

$R^3$  and  $R^4$

are independent of one another are identical or different and are

1) hydrogen atom,

2) halogen,

3)  $-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or substituted one to three times by  $R^{13}$ ,

4)  $-(C_1-C_3)$ -perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by  $R^{13}$ ,

6)  $-O-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or substituted one to three times by  $R^{13}$ ,

7)  $-CN$ ,

8)  $-OH$ ,

9)  $-C(O)-O-R^{11}$ ,

10)  $-(C_0-C_4)$ alkyl- $C(O)-N-R^{11}R^{12}$ ,

11)  $-NR^{11}R^{12}$ ,

12)  $-NR^{10}-SO_2-R^{10}$ ,

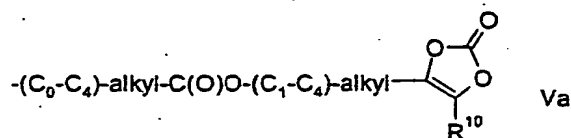
13)  $-SO_n-R^{10}$ , wherein n is 1 or 2,

14)  $-SO_2-NR^{11}R^{12}$ ,

15)  $-C(O)-O-C(R^{15}R^{16})-O-C(O)-R^{17}$ , wherein  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are as defined above,

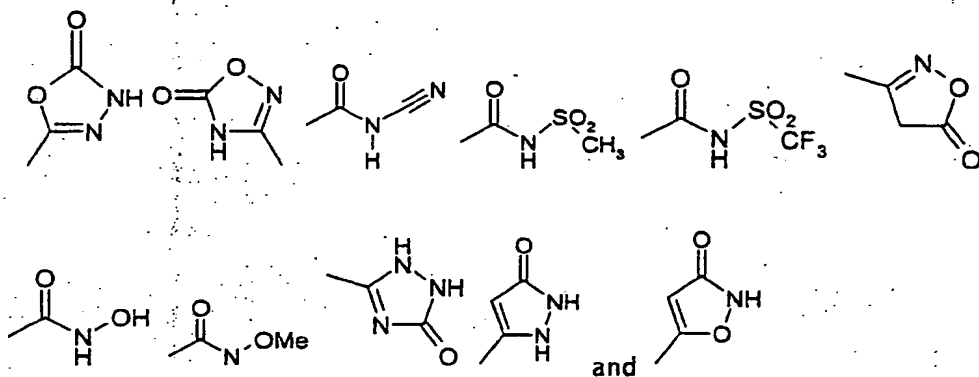
16)  $-C(O)-O-C(R^{15}R^{16})-O-C(O)-O-R^{17}$ , wherein  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are as defined above,

17) residue of formula Va,

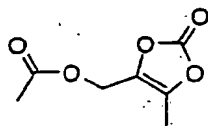


10 wherein R<sup>10</sup> is defined as above,

- 18) -NR<sup>10</sup>-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,  
 19) -OCF<sub>3</sub>, or  
 20) a residue from the following list



- 21) -(C<sub>0</sub>-C<sub>2</sub>)-alkyl-C(O)-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-O-C(O)-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,  
 22) -(C<sub>0</sub>-C<sub>2</sub>)-alkyl-C(O)-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl-O-C(O)O-(C<sub>1</sub>-C<sub>7</sub>)-alkyl, or  
 23)



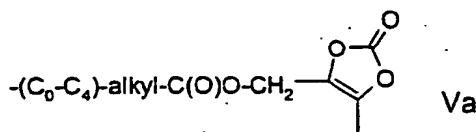
wherein R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>15</sup>, R<sup>16</sup> or R<sup>17</sup> are as defined above,  
 in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

45 5) The present invention also relates to the compounds of the formula I, wherein

- R<sup>0</sup> is
1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by R<sup>8</sup>, or
  2. a monocyclic 4- to 14-membered heteroaryl out of the group thienyl, thiadiazolyl, isoxazolyl and thiazolyl, wherein said heteroaryl is substituted by a residue selected out of the group thiophenyl, thienyl, 2-thienyl and 3-thienyl, wherein said residue is unsubstituted or mono- or disubstituted independently of one another by R<sup>8</sup>, R<sup>8</sup> is F, Cl, Br, -OCH<sub>3</sub>, -C(O)-NH<sub>2</sub> or -OCF<sub>3</sub>,

55 Q is a direct bond, -C(O)-, -SO<sub>2</sub>-, methylene or ethylene,  
 R<sup>1</sup> is a hydrogen atom,  
 R<sup>2</sup> is a direct bond or methylene, or

$R^1-N-R^2-V$  can form a 4- to 7-membered cyclic group out of the group azetidine, pyrrolidine, piperidine and piperazine,  $R^{13}$  is  $-OH$ ,  $=O$ ,  $-F$ ,  $-CF_3$ ,  $-C(O)-O-R^{11}$ ,  $-C(O)-N-R^{11}R^{12}$ ,  $-NR^{11}R^{12}$ ,  $-NR^{10}-SO_2-R^{10}$ ,  $-SO_n-R^{10}$ , wherein  $n$  is 1, 2 or 3;  $-(C_1-C_6)$ -alkyl,  $-(C_0-C_3)$ -alkyl- $O-(C_0-C_4)$ -alkyl,  $-SO_2-NR^{11}R^{12}$ ,  $-C(O)-R^{10}$ ,  $-(C_0-C_4)$ -alkyl- $C(O)-O-C(R^{15}R^{16})-O-C(O)-R^{17}$ ,  $-(C_0-C_4)$ -alkyl- $C(O)-O-C(R^{15}R^{16})-O-C(O)-R^{17}$ , or a residue of formula Va,



wherein  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{15}$ ,  $R^{16}$  or  $R^{17}$  are as defined above,  
 $R^{14}$  is halogen, methyl, ethyl or  $-NH_2$ ,

V is 1. a residue out of the group containing compounds which is derived from isoquinoline, quinoline, quina-  
 zoline, piperidine, azetidine, pyrrolidine, tetrahydropyran, piperazine and isoxazole,  
 wherein said cyclic residue is unsubstituted or mono- or disubstituted independently of one another by  
 $R^{14}$ , or

2. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by  
 $R^{14}$ , or

G is a direct bond,  $-(CH_2)_m-$ , or  $-(CH_2)_m-NR^{10}-$ ,

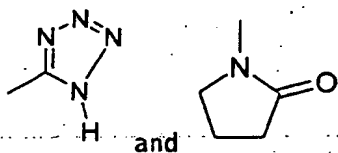
$m$  is the integers zero, 1 or 2,

$R^{10}$  is hydrogen atom or  $-(C_1-C_4)$ -alkyl,

M is a hydrogen atom,  $(C_2-C_4)$ -alkyl, imidazolyl, pyrazolyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, pyrid-  
 inyl, pyrimidyl, pyrazinyl, pyridazinyl, or  $(C_3-C_6)$ -cycloalkyl, wherein said cyclic residues are unsubsti-  
 tuted or mono- or disubstituted independently of one another by  $R^{14}$

$R^{11}$  and  $R^{12}$  together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered  
 monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or  
 different ring heteroatoms chosen from oxygen, sulfur and nitrogen out of the group azaspirodecane,  
 azetidine, dihydrooxazole, imidazolidine, morpholine, oxazolidine, oxazepane, piperazine, piperidine,  
 pyrazole, pyrrolidine, thiazolidine, thiomorpholine or thiophenyl, wherein said heterocyclic ring is un-  
 substituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ,

$R^{13}$  is  $Cl$ ,  $-CN$ ,  $=O$ ,  $-(C_0-C_2)$ -alkyl- $OH$ ,  $-(C_1-C_2)$ -alkyl,  $-(C_1-C_2)$ -alkoxy,  $-(C_3-C_6)$ -cycloalkyl,  $-(C_0-C_2)$ -alkyl- $CF_3$ ,  
 $-(C_0-C_2)$ -alkyl- $C(O)-O-R^{11}$ ,  $-(C_0-C_2)$ -alkyl- $C(O)-N(R^{11})-R^{12}$ ,  $-(C_0-C_2)$ -alkyl- $N(R^{11})-R^{12}$ ,  $S(O)_2-CH_3$ ,  
 $-(C_0-C_2)$ -alkyl- $Si-(CH_3)_3$ ,  $-(C_0-C_2)$ -alkyl- $S(O)_2-(C_0-C_4)$ -alkyl,  $-(C_0-C_4)$ -alkyl- $S(O)_2-N(R^{11})-R^{12}$ ,  
 $-(C_1-C_2)$ -alkylene- $O-(C_1-C_2)$ -alkyl or a residue from the following list



$R^3$  and  $R^4$  are independent of one another are identical or different and are

a) hydrogen atom,

b)  $F$ ,  $Cl$ ,

c)  $-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or substituted by  $R^{13}$ ,

d) phenyl, wherein phenyl is unsubstituted or substituted one to three times by  $R^{13}$ ,

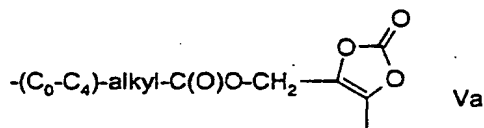
e)  $-O-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or substituted by  $R^{13}$ ,

f)  $-C(O)-O-R^{11}$ ,

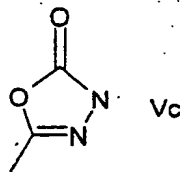
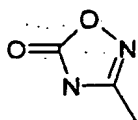
g)  $-(C_0-C_2)$ -alkyl- $C(O)-N-R^{11}R^{12}$ ,

h)  $-NR^{11}R^{12}$ ,

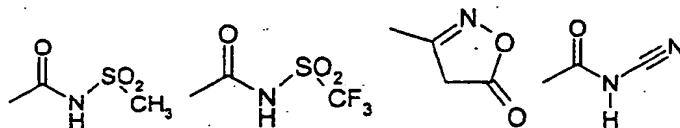
- l)  $-\text{NR}^{10}-\text{SO}_2-\text{R}^{10}$ ,  
 j)  $-\text{SO}_2-\text{NR}^{11}\text{R}^{12}$ ,  
 k)  $-\text{C}(\text{O})-\text{R}^{10}$   
 l)  $-\text{C}(\text{O})-\text{O}-\text{C}(\text{R}^{15}\text{R}^{16})-\text{O}-\text{C}(\text{O})-\text{R}^{17}$ , wherein  $\text{R}^{15}$ ,  $\text{R}^{16}$  and  $\text{R}^{17}$  are as defined above,  
 m)  $-\text{C}(\text{O})-\text{O}-\text{C}(\text{R}^{15}\text{R}^{16})-\text{O}-\text{C}(\text{O})\text{O}-\text{R}^{17}$ , wherein  $\text{R}^{15}$ ,  $\text{R}^{16}$  and  $\text{R}^{17}$  are as defined above,  
 n) a residue of formula Va



- o) a residue of formula Vb or Vc,



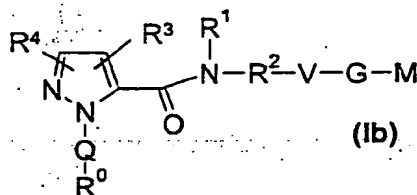
- p) a residue from the following list



- 35
- q)  $-\text{CN}$  or  
 -r)  $\text{CF}_3$

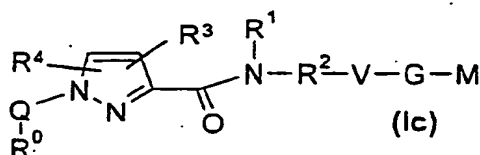
in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

[0008] The present invention also relates to the compounds of the formula Ib,



wherein  $\text{R}^0$ ;  $\text{R}^1$ ;  $\text{R}^2$ ;  $\text{R}^3$ ;  $\text{R}^4$ ; Q; V, G and M have the meanings indicated in formula I.

[0009] The present invention also relates to the compounds of the formula Ic,



wherein R<sup>0</sup>; R<sup>1</sup>; R<sup>2</sup>; R<sup>3</sup>; R<sup>4</sup>; Q; V, G and M have the meanings indicated in formula I.

[0010] The present invention also relates to the compounds of the formula I, which are

- 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 2-(6-Chloro-benzothiazol-2-yl)-5-methyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 5-(5-Chloro-thiophen-2-yl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 5-(5-Chloro-thiophen-2-yl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(2,4-dichloro-phenyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-propyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-propyl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 5-tert-Butyl-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 5-tert-Butyl-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-propyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-propyl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 2-[2-(5-Chloro-thiophen-2-yl)-thiazol-4-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 1-[2-(5-Chloro-thiophen-2-yl)-thiazol-4-ylmethyl]-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 2-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 1-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide
- 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-amide
- 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-amide
- 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-ylmethyl)-amide

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-1H-pyrazole-3- carboxylic acid (1-isopropyl-pi-  
 peridin-4-ylmethyl)-amide  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3- carboxylic acid (3,4,5,6-tetra-  
 hydro-2H-[1,4']bipyridinyl-4-yl)-amide  
 5 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-1H-pyrazole-3- carboxylic acid (3,4,5,6-tetra-  
 hydro-2H-[1,4']bipyridinyl-4-yl)-amide  
 2-(4-Chloro-benzyl)-4-cyano-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-(4-Chloro-benzyl)-4-cyano-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 10 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-pyrazole-3-carbo-  
 xylic acid methyl ester  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4- ylcarbamoyl)-2H-pyrazole-3-carbo-  
 xylic acid methyl ester  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-pyrazole-3-carbo-  
 xylic acid  
 15 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4- ylcarbamoyl)-2H-pyrazole-3-carbo-  
 xylic acid  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-pyrazole-3-carbo-  
 xylic acid ethyl ester  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4- ylcarbamoyl)-2H-pyrazole-3-carbo-  
 xylic acid ethyl ester  
 20 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(morpholine-4-carbonyl)-2H- pyrazole-3-carboxylic acid (1-  
 isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(morpholine-4-carbonyl)-1H- pyrazole-3-carboxylic acid (1-  
 isopropyl-piperidin-4-yl)-amide  
 25 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-dimethylamide 5-[(1-iso-  
 propyl-piperidin-4-yl)-amide]  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-yl methyl]-1H-pyrazole-3,5-dicarboxylic acid 5-dimethylamide 3-[(1-iso-  
 propyl-piperidin-4-yl)-amide]  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- [(2-hydroxy-ethyl)-amide]  
 30 5-[(1-isopropyl-piperidin-4-yl)-amide]  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(2-hydroxy-ethyl)-amide]  
 3-[(1-isopropyl-piperidin-4-yl)-amide]  
 {[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carb-  
 onyl]-amino}-acetic acid  
 35 {[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4- ylcarbamoyl)-2H-pyrazole-3-carb-  
 onyl]-amino}-acetic acid  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(5-oxo-4,5-dihydro-[1,3,4]oxadiazol- 2-yl)-2H-pyrazole-3-  
 carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(5-oxo-4,5-dihydro-[1,3,4]oxadiazol- 2-yl)-1H-pyrazole-3-  
 40 carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 Sulfuric acid mono-(2-[[1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarba-  
 moyl)-1H-pyrazole-3-carbonyl]-amino]-ethyl) ester  
 Sulfuric acid mono-(2-[[2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarba-  
 moyl)-2H-pyrazole-3-carbonyl]-amino]-ethyl) ester  
 45 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[4-(2-hydroxy-ethyl)-piperazine-1- carbonyl]-2H-pyrazole-3-  
 carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[4-(2-hydroxy-ethyl)-piperazine-1- carbonyl]-1H-pyrazole-3-  
 carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-oxo-oxazolidine-3-carbonyl)-2H- pyrazole-3-carboxylic acid  
 50 (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-oxo-oxazolidine-3-carbonyl)-1H- pyrazole-3-carboxylic acid  
 (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1-isopropyl-piperidin-4-  
 yl)-amide] 3-[(2-morpholin-4-yl-ethyl)-amide]  
 55 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- [(1-isopropyl-piperidin-4-  
 yl)-amide] 5-[(2-morpholin-4-yl-ethyl)-amide]  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- [bis-(2-methoxy-ethyl)-amide]  
 5-[(1-isopropyl-piperidin-4-yl)-amide]

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [bis-(2-methoxy-ethyl)-amide] 3-[(1-isopropyl-piperidin-4-yl)-amide]  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- [(4,5-dihydro-oxazol-2-yl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide]  
 5 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(4,5-dihydro-oxazol-2-yl)-amide] 3-[(1-isopropyl-piperidin-4-yl)-amide]  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)- amide  
 10 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-methoxymethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3- carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-methoxymethyl-pyrrolidine-1- carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 15 {[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-pyrazole-3-carbon-yl]-methyl-amino}-acetic acid  
 {[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4- ylcarbamoyl)-2H-pyrazole-3-carbon-yl]-methyl-amino}-acetic acid  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4- ylcarbamoyl)-1H-pyrazole-3-carbonyl]-piperidine-4-carboxylic acid ethyl ester  
 20 1-[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4- ylcarbamoyl)-2H-pyrazole-3-carbonyl]-piperidine-4-carboxylic acid ethyl ester  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-azetidine-2-carboxylic acid  
 25 1-[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carbonyl]-azetidine-2-carboxylic acid  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(thiomorpholine-4-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(thiomorpholine-4-carbonyl)-1H- pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 30 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-pyrrolidine-2-carboxylic acid  
 1-[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carbonyl]-pyrrolidine-2-carboxylic acid  
 35 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4-hydroxy-piperidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4-hydroxy-piperidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxymethyl-pyrrolidine-1- carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 40 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxymethyl-pyrrolidine-1- carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-pyrrolidine-1-carbonyl)- 2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 45 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-pyrrolidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 5-(2,5-Bis-methoxymethyl-pyrrolidine-1-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 5-(2,5-Bis-methoxymethyl-pyrrolidine-1-carbonyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 50 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4-hydroxymethyl-piperidine-1- carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4-hydroxymethyl-piperidine-1- carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 55 5-(8-Aza-spiro[4.5]decane-8-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]- 2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 5-(8-Aza-spiro[4.5]decane-8-carbonyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]- 1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-methanesulfonyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-methanesulfonyl-pyrrolidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 5 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- [(1,1-dioxo-tetrahydro-1-thiophen-3-yl)-methyl-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide]  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1,1-dioxo-tetrahydro-1-thiophen-3-yl)-methyl-amide] 3-[(1-isopropyl-piperidin-4-yl)-amide].  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbonyl)-1H-pyrazole-3-carbonyl]-azetidine-3-carboxylic acid  
 10 1-[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbonyl)-2H-pyrazole-3-carbonyl]-azetidine-3-carboxylic acid  
 5-(Azetidine-1-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 15 5-(Azetidine-1-carbonyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-oxo-piperazine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-oxo-piperazine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 20 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4,4-difluoro-piperidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4,4-difluoro-piperidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 25 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[(1,4)oxazepane-4-carbonyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[(1,4)oxazepane-4-carbonyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 30 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-trifluoromethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 35 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-trifluoromethyl-pyrrolidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2,2-dimethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2,2-dimethyl-pyrrolidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 40 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1-isopropyl-piperidin-4-yl)-amide] 3-[(2-sulfamoyl-ethyl)-amide]  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- [(1-isopropyl-piperidin-4-yl)-amide] 5-[(2-sulfamoyl-ethyl)-amide]  
 45 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-cyclopropylamide 5-[(1-isopropyl-piperidin-4-yl)-amide]  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-cyclopropylamide 3-[(1-isopropyl-piperidin-4-yl)-amide]  
 50 {[(1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbonyl)-1H-pyrazole-3-carbonyl]-amino)-methanesulfonic acid  
 {[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbonyl)-2H-pyrazole-3-carbonyl]-amino)-methanesulfonic acid  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-cyclobutylamide 5-[(1-isopropyl-piperidin-4-yl)-amide]  
 55 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-cyclobutylamide 3-[(1-isopropyl-piperidin-4-yl)-amide]  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1-isopropyl-piperidin-4-yl)-amide] 3-[(2-methoxy-ethyl)-amide]



1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- [(1-isopropyl-piperidin-4-yl)-amide] 5-[(2-methoxy-ethyl)-amide]  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 5 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(pyrrolidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(cyanamide-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(cyanamide-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 10 Phosphoric acid mono-(2-[(1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl)-amino]-ethyl) ester  
 Phosphoric acid mono-(2-[(2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carbonyl)-amino]-ethyl) ester  
 15 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid methyl ester  
 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid  
 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-pyrazole-3,5-dicarboxylic acid 3- cyclobutylamide 5-[(1-isopropyl-piperidin-4-yl)-amide]  
 20 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid bis-[(1-isopropyl-piperidin-4-yl)-amide]  
 25 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 2-[(4-Chloro-phenylcarbamoyl)-methyl]-4-cyano-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 30 3-[(1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl)-amino]-propionic acid  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1-isopropyl-piperidin-4-yl)-amide] 3-(methoxy-amide)  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-carbamoylmethyl-amide  
 35 5-[(1-isopropyl-piperidin-4-yl)-amide]  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-amino)-acetic acid ethyl ester  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- [(3-hydroxy-propyl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide]  
 40 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-2S)-azetidine-2-carboxylic acid  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2S,2-hydroxymethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-2S-pyrrolidine-2-carboxylic acid  
 45 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2S,2-methoxymethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 5-(2R,5R,2,5-Bis-methoxymethyl-pyrrolidine-1-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 50 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- [(4,5-dihydro-oxazol-2-yl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide]  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-piperidine-4-carboxylic acid ethyl ester  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1-isopropyl-piperidin-4-yl)-amide] 3-[(2-morpholin-4-yl-ethyl)-amide]  
 55 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4,4-difluoro-piperidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-oxo-oxazolidine-3-carbonyl)-2H-pyrazole-3-carboxylic acid

(1-isopropyl-piperidin-4-yl)-amide

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1-isopropyl-piperidin-4-yl)-amide] 3-[(2-(2-oxo-imidazolidin-1-yl)-ethyl)-amide]

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1-isopropyl-piperidin-4-yl)-amide] 3-[(2,2,2-trifluoro-ethyl)-amide]

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- [(1,1-dioxo-tetrahydro-1-thiophen-3-yl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide]

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1-isopropyl-piperidin-4-yl)-amide] 3-[(3-(2-oxo-pyrrolidin-1-yl)-propyl)-amide]

5-(Azetidine-1-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(thiazolidine-3-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

2-[[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-amino]-3,3,3-trifluoro-propionic acid

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1-isopropyl-piperidin-4-yl)-amide] 3-trimethylsilylmethyl-amide

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[4-(2-oxo-pyrrolidin-1-yl)-piperidine-1-carbonyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methanesulfonylamino-carbonyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0011]** In general, the meaning of any group, residue, heteroatom, number etc., which can occur more than once in the compounds of the formula I, is independent of the meaning of this group, residue, heteroatom, number etc. in any other occurrence. All groups, residues, heteroatoms, numbers etc., which can occur more than once in the compounds of the formula I can be identical or different.

**[0012]** As used herein, the term alkyl is to be understood in the broadest sense to mean hydrocarbon residues which can be linear, i. e. straight-chain, or branched and which can be acyclic or cyclic residues or comprise any combination of acyclic and cyclic subunits. Further, the term alkyl as used herein expressly includes saturated groups as well as unsaturated groups which latter groups contain one or more, for example one, two or three, double bonds and/or triple bonds, provided that the double bonds are not located within a cyclic alkyl group in such a manner that an aromatic system results. All these statements also apply if an alkyl group occurs as a substituent on another residue, for example in an alkoxy residue, an alkoxy-carbonyl residue or an arylalkyl residue. Examples of "-(C<sub>1</sub>-C<sub>8</sub>)-alkyl" or "-(C<sub>1</sub>-C<sub>8</sub>)-alkylene" are alkyl residues containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms are methyl, methylene, ethyl, ethylene, propyl, propylene, butyl, butylene, pentyl, pentylene, hexyl, heptyl or octyl, the n-isomers of all these residues, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tBu, tert-pentyl, sec-butyl, tert-butyl or tert-pentyl. The term "-(C<sub>0</sub>-C<sub>8</sub>)-alkyl" or "-(C<sub>0</sub>-C<sub>8</sub>)-alkylene" is a hydrocarbon residues containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms. The term "C<sub>0</sub>-alkyl" or "C<sub>0</sub>-alkylene" is a covalent bond.

**[0013]** Unsaturated alkyl residues are, for example, alkenyl residues such as vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl or 1,3-pentadienyl, or alkynyl residues such as ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butylnyl. Alkyl residues can also be unsaturated when they are substituted.

**[0014]** Examples of -(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl cyclic alkyl residues are cycloalkyl residues containing 3, 4, 5, 6, 7 or 8 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, which can also be substituted and/or unsaturated. Unsaturated cyclic alkyl groups and unsaturated cycloalkyl groups like, for example, cyclopentenyl or cyclohexenyl can be bonded via any carbon atom.

**[0015]** Of course, a cyclic alkyl group has to contain at least three carbon atoms, and an unsaturated alkyl group has to contain at least two carbon atoms. Thus, a group like (C<sub>1</sub>-C<sub>8</sub>)-alkyl is to be understood as comprising, among others, saturated acyclic (C<sub>1</sub>-C<sub>8</sub>)-alkyl, (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, and unsaturated (C<sub>2</sub>-C<sub>8</sub>)-alkyl like (C<sub>2</sub>-C<sub>8</sub>)-alkenyl or (C<sub>2</sub>-C<sub>8</sub>)-alkynyl. Similarly, a group like (C<sub>1</sub>-C<sub>4</sub>)-alkyl is to be understood as comprising, among others, saturated acyclic (C<sub>1</sub>-C<sub>4</sub>)-alkyl, and unsaturated (C<sub>2</sub>-C<sub>4</sub>)-alkyl like (C<sub>2</sub>-C<sub>4</sub>)-alkenyl or (C<sub>2</sub>-C<sub>4</sub>)-alkynyl.

**[0016]** Unless stated otherwise, the term alkyl preferably comprises acyclic saturated hydro-carbon residues which have from one to six carbon atoms and which can be linear or branched. A particular group of saturated acyclic alkyl residues is formed by (C<sub>1</sub>-C<sub>4</sub>)-alkyl residues like methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tBu.

**[0017]** Unless stated otherwise, and irrespective of any specific substituents bonded to alkyl groups which are indicated in the definition of the compounds of the formula I, alkyl groups can in general be unsubstituted or substituted

by one or more, for example one, two or three, identical or different substituents. Any kind of substituents present in substituted alkyl residues can be present in any desired position provided that the substitution does not lead to an unstable molecule. Examples of substituted alkyl residues are alkyl residues in which one or more, for example 1, 2 or 3, hydrogen atoms are replaced with halogen atoms, in particular fluorine atoms.

**[0018]** The term "mono- or bicyclic 4- to 15-membered heteroaryl" or " $-(C_4-C_{15})$ -heteroaryl" refers to  $(C_4-C_{15})$ -aryl in which one or more of the 4 to 15 ring carbon atoms are replaced by heteroatoms such as nitrogen, oxygen or sulfur. Examples are acridinyl, azetidyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolyl, indolyl, decahydrochinolyl, 2H, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuran, fuananyl, furazanyl, imidazolidinyl, imidazolyl, imidazolyl, 1H-indazolyl, indolyl, indolizyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolyl, isoindolyl, isoquinolyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridoaxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolyl, quinolyl, 4H-quinolizyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisochinolyl, tetrahydrochinolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

Preferred are pyridyl; such as 2-pyridyl, 3-pyridyl or 4-pyridyl; pyrrolyl; such as 2-pyrrolyl and 3-pyrrolyl; furyl; such as 2-furyl and 3-furyl; thienyl; such as 2-thienyl and 3-thienyl; imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl; tetrazolyl, pyridazinyl, pyrazinyl, pyrimidinyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolyl, isoquinolyl, chromanyl, isochromanyl, cinnolyl, quinazolyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl.

**[0019]** The term " $R^1-N-R^2-V$  can form a 4- to 7-membered cyclic group" refers to structures of heterocycles which can be derived from compounds such as piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine.

**[0020]** The term " $R_{15}$  and  $R_{16}$  are together with the carbon atom to which they are bonded they form a 3- to 6 membered carbocyclic ring" refers to  $(C_3-C_6)$ -cycloalkyl structures such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms" refers to structures of heterocycles which can be derived from compounds such as, aziridine, azirine, azetidine, pyrrole, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine.

The term "het" refers to structures of heterocycles which can be derived from compounds such as, aziridine, azirine, azetidine, pyrrole, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine.

**[0021]** The term " $R_{11}$  and  $R_{12}$  together with the nitrogen atom to which they are bonded can form a saturated or unsaturated 4- to 7-membered monocyclic heterocyclic ring" refers to residues which can be derived from compounds such as azetidine, azetidinone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine.

**[0022]** The fact that many of the before-listed names of heterocycles are the chemical names of unsaturated or aromatic ring systems does not imply that the 4-15 membered mono- or polycyclic group could only be derived from the respective unsaturated ring system. The names here only serve to describe the ring system with respect to ring size and the number of the heteroatoms and their relative positions. As explained above, the 4-15 membered

mono- or polycyclic group can be saturated or partially unsaturated or aromatic, and can thus be derived not only from the before-listed heterocycles themselves but also from all their partially or completely hydrogenated analogues and also from their more highly unsaturated analogues if applicable. As examples of completely or partially hydrogenated analogues of the before-listed heterocycles from which this group may be derived the following may be mentioned:

pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, piperidine, 1,3-dioxolane, 2-imidazoline, imidazolidine, 4,5-dihydro-1,3-oxazol, 1,3-oxazolidine, 4,5-dihydro-1,3-thiazole, 1,3-thiazolidine, perhydro-1,4-dioxane, piperazine, perhydro-1,4-oxazine (= morpholine), perhydro-1,4-thiazine (= thiomorpholine), perhydroazepine, indoline, isoindoline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, etc.

**[0023]** The 4-15 membered mono- or polycyclic group may be bonded via any ring carbon atom, and in the case of nitrogen heterocycles via any suitable ring nitrogen atom. Thus, for example, a pyrrolyl residue can be 1-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, a pyrrolidinyl residue can be pyrrolidin-1-yl (= pyrrolidino), pyrrolidin-2-yl or pyrrolidin-3-yl, a pyridinyl residue can be pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, a piperidinyl residue can be piperidin-1-yl (= piperidino), piperidin-2-yl, piperidin-3-yl or piperidin-4-yl. Furyl can be 2-furyl or 3-furyl, thienyl can be 2-thienyl or 3-thienyl, imidazolyl can be imidazol-1-yl, imidazol-2-yl, imidazol-4-yl or imidazol-5-yl, 1,3-oxazolyl can be 1,3-oxazol-2-yl, 1,3-oxazol-4-yl or 1,3-oxazol-5-yl, 1,3-thiazolyl can be 1,3-thiazol-2-yl, 1,3-thiazol-4-yl or 1,3-thiazol-5-yl, pyrimidinyl can be pyrimidin-2-yl, pyrimidin-4-yl (= 6-pyrimidinyl) or 5-pyrimidinyl, piperazinyl can be piperazin-1-yl (= piperazino) or piperazin-2-yl. Indolyl can be indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl or indol-7-yl. Similarly benzimidazolyl, benzoxazolyl and benzothiazol residues can be bonded via the 2-position and via any of the positions 4, 5, 6, and 7. Quinolinyl can be quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl or quinolin-8-yl, isoquinolinyl can be isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl or isoquinolin-8-yl. In addition to being bonded via any of the positions indicated for quinolinyl and isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl and 1,2,3,4-tetrahydroisoquinolinyl can also be bonded via the nitrogen atoms in 1-position and 2-position, respectively.

Unless stated otherwise, and irrespective of any specific substituents bonded to the 4-15 membered mono- or polycyclic group or any other heterocyclic groups which are indicated in the definition of the compounds of the formula I, the 4-15 membered mono- or polycyclic group can be unsubstituted or substituted on ring carbon atoms with one or more, for example one, two, three, four or five, identical or different substituents like (C<sub>1</sub>-C<sub>8</sub>)-alkyl, in particular (C<sub>1</sub>-C<sub>4</sub>)-alkyl, (C<sub>1</sub>-C<sub>8</sub>)-alkyloxy, in particular (C<sub>1</sub>-C<sub>4</sub>)-alkyloxy, (C<sub>1</sub>-C<sub>4</sub>)-alkylthio, halogen, nitro, amino, ((C<sub>1</sub>-C<sub>4</sub>)-alkyl)carbonylamino like acetylamino, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, hydroxy-(C<sub>1</sub>-C<sub>4</sub>)-alkyl such as, for example, hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl, methylenedioxy, ethylenedioxy, formyl, acetyl, cyano, aminosulfonyl, methylsulfonyl, hydroxycarbonyl, aminocarbonyl, (C<sub>1</sub>-C<sub>4</sub>)-alkyloxycarbonyl, optionally substituted phenyl, optionally substituted phenoxy, benzyl optionally substituted in the phenyl group, benzyloxy optionally substituted in the phenyl group, etc. The substituents can be present in any desired position provided that a stable molecule results. Of course an oxo group cannot be present in an aromatic ring. Each suitable ring nitrogen atom in the 4-15 membered mono- or polycyclic group can independently of each other be unsubstituted, i. e. carry a hydrogen atom, or can be substituted, i. e. carry a substituent like (C<sub>1</sub>-C<sub>8</sub>)-alkyl, for example (C<sub>1</sub>-C<sub>4</sub>)-alkyl such as methyl or ethyl, optionally substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, for example benzyl, optionally substituted in the phenyl group, hydroxy-(C<sub>2</sub>-C<sub>4</sub>)-alkyl such as, for example 2-hydroxyethyl, acetyl or another acyl group, methylsulfonyl or another sulfonyl group, aminocarbonyl, (C<sub>1</sub>-C<sub>4</sub>)-alkyloxycarbonyl, etc. In general, in the compounds of the formula I nitrogen heterocycles can also be present as N-oxides or as quaternary salts. Ring sulfur atoms can be oxidized to the sulfoxide or to the sulfone. Thus, for example a tetrahydrothienyl residue may be present as S,S-dioxotetrahydro-thienyl residue or a thiomorpholinyl residue like thiomorpholin-4-yl may be present as 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl. A substituted 4 to 15 membered mono- or polycyclic group that can be present in a specific position of the compounds of formula I can independently of other groups be substituted by substituents selected from any desired subgroup of the substituents listed before and/or in the definition of that group.

**[0024]** The 3-7 membered monocyclic group may be bonded via any ring carbon atom, and in the case of nitrogen heterocycles via any suitable ring nitrogen atom. Thus, for example, a pyrrolyl residue can be 1-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, a pyrrolidinyl residue can be pyrrolidin-1-yl (= pyrrolidino), pyrrolidin-2-yl or pyrrolidin-3-yl, a pyridinyl residue can be pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, a piperidinyl residue can be piperidin-1-yl (= piperidino), piperidin-2-yl, piperidin-3-yl or piperidin-4-yl. Furyl can be 2-furyl or 3-furyl, thienyl can be 2-thienyl or 3-thienyl, imidazolyl can be imidazol-1-yl, imidazol-2-yl, imidazol-4-yl or imidazol-5-yl, 1,3-oxazolyl can be 1,3-oxazol-2-yl, 1,3-oxazol-4-yl or 1,3-oxazol-5-yl, 1,3-thiazolyl can be 1,3-thiazol-2-yl, 1,3-thiazol-4-yl or 1,3-thiazol-5-yl, pyrimidinyl can be pyrimidin-2-yl, pyrimidin-4-yl (= 6-pyrimidinyl) or 5-pyrimidinyl, piperazinyl can be piperazin-1-yl (= piperazino) or piperazin-2-yl. Unless stated otherwise, and irrespective of any specific substituents bonded to the 3-7 membered monocyclic group or any other heterocyclic groups which are indicated in the definition of the compounds of the formula I, can be unsubstituted or substituted on ring carbon atoms with one or more, for example one, two, three, four or five, identical or different substituents like (C<sub>1</sub>-C<sub>8</sub>)-alkyl, in particular (C<sub>1</sub>-C<sub>4</sub>)-alkyl, (C<sub>1</sub>-C<sub>8</sub>)-alkyloxy, in particular (C<sub>1</sub>-C<sub>4</sub>)-alkyloxy, (C<sub>1</sub>-C<sub>4</sub>)-alkylthio, halogen, nitro, amino, ((C<sub>1</sub>-C<sub>4</sub>)-alkyl)carbonylamino like acetylamino, trifluoromethyl, trif-

luoromethoxy, hydroxy, oxo, hydroxy-(C<sub>1</sub>-C<sub>4</sub>)-alkyl such as, for example, hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl, methylenedioxy, ethylenedioxy, formyl, acetyl, cyano, aminosulfonyl, methylsulfonyl, hydroxycarbonyl, aminocarbonyl, (C<sub>1</sub>-C<sub>4</sub>)-alkyloxycarbonyl, optionally substituted phenyl, optionally substituted phenoxy, benzyl optionally substituted in the phenyl group, benzyloxy optionally substituted in the phenyl group, etc. The substituents can be present in any desired position provided that a stable molecule results. Of course an oxo group cannot be present in an aromatic ring. Each suitable ring nitrogen atom in the 3-7 membered monocyclic group can independently of each other be unsubstituted, i. e. carry a hydrogen atom, or can be substituted, i. e. carry a substituent like (C<sub>1</sub>-C<sub>8</sub>)-alkyl, for example (C<sub>1</sub>-C<sub>4</sub>)-alkyl such as methyl or ethyl, optionally substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, for example benzyl, optionally substituted in the phenyl group, hydroxy-(C<sub>2</sub>-C<sub>4</sub>)-alkyl such as, for example 2-hydroxyethyl, acetyl or another acyl group, methylsulfonyl or another sulfonyl group, aminocarbonyl, (C<sub>1</sub>-C<sub>4</sub>)-alkyloxycarbonyl, etc. In general, in the compounds of the formula I nitrogen heterocycles can also be present as N-oxides or as quaternary salts. Ring sulfur atoms can be oxidized to the sulfoxide or to the sulfone. Thus, for example a tetrahydrothienyl residue may be present as S, S-dioxotetrahydrothienyl residue or a thiomorpholinyl residue like thiomorpholin-4-yl may be present as 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl. A substituted 3-7 membered monocyclic group that can be present in a specific position of the compounds of formula I can independently of other groups be substituted by substituents selected from any desired subgroup of the substituents listed before and/or in the definition of that group.

**[0025]** Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, particularly preferably chlorine or bromine.

**[0026]** Optically active carbon atoms present in the compounds of the formula I can independently of each other have R configuration or S configuration. The compounds of the formula I can be present in the form of pure enantiomers or pure diastereomers or in the form of mixtures of enantiomers and/or diastereomers, for example in the form of racemates. The present invention relates to pure enantiomers and mixtures of enantiomers as well as to pure diastereomers and mixtures of diastereomers. The invention comprises mixtures of two or of more than two stereoisomers of the formula I, and it comprises all ratios of the stereoisomers in the mixtures.

**[0027]** In case the compounds of the formula I can be present as E isomers or Z isomers (or cis isomers or trans isomers) the invention relates both to pure E isomers and pure Z isomers and to E/Z mixtures in all ratios. The invention also comprises all tautomeric forms of the compounds of the formula I.

**[0028]** Diastereomers, including E/Z isomers, can be separated into the individual isomers, for example, by chromatography. Racemates can be separated into the two enantiomers by customary methods, for example by chromatography on chiral phases or by resolution, for example by crystallization of diastereomeric salts obtained with optically active acids or bases. Stereochemically uniform compounds of the formula I can also be obtained by employing stereochemically uniform starting materials or by using stereoselective reactions.

**[0029]** Physiologically tolerable salts of the compounds of formula I are nontoxic salts that are physiologically acceptable, in particular pharmaceutically utilizable salts. Such salts of compounds of the formula I containing acidic groups, for example a carboxyl group COOH, are for example alkali metal salts or alkaline earth metal salts such as sodium salts, potassium salts, magnesium salts and calcium salts, and also salts with physiologically tolerable quaternary ammonium ions such as tetramethylammonium or tetraethylammonium, and acid addition salts with ammonia and physiologically tolerable organic amines, such as methylamine, dimethylamine, trimethylamine, ethylamine, triethylamine, ethanolamine or tris-(2-hydroxyethyl)amine. Basic groups contained in the compounds of the formula I, for example amino groups or guanidino groups, form acid addition salts, for example with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid, or with organic carboxylic acids and sulfonic acids such as formic acid, acetic acid, oxalic acid, citric acid, lactic acid, malic acid, succinic acid, malonic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or p-toluenesulfonic acid. Compounds of the formula I which simultaneously contain a basic group and an acidic group, for example a guanidino group and a carboxyl group, can also be present as zwitterions (betaines) which are likewise included in the present invention.

**[0030]** Salts of compounds of the formula I can be obtained by customary methods known to those skilled in the art, for example by combining a compound of the formula I with an inorganic or organic acid or base in a solvent or dispersant, or from other salts by cation exchange or anion exchange. The present invention also includes all salts of the compounds of the formula I which, because of low physiological tolerability, are not directly suitable for use in pharmaceuticals but are suitable, for example, as intermediates for carrying out further chemical modifications of the compounds of the formula I or as starting materials for the preparation of physiologically tolerable salts.

The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols.

The invention also includes derivatives and modifications of the compounds of the formula I, for example prodrugs, protected forms and other physiologically tolerable derivatives, as well as active metabolites of the compounds of the formula I. The invention relates in particular to prodrugs and protected forms of the compounds of the formula I, which can be converted into compounds of the formula I under physiological conditions. Suitable prodrugs for the compounds of the formula I, i. e. chemically modified derivatives of the compounds of the formula I having properties which are

improved in a desired manner, for example with respect to solubility, bioavailability or duration of action, are known to those skilled in the art. More detailed information relating to prodrugs is found in standard literature like, for example, Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Fleisher et al., Advanced Drug Delivery Reviews 19 (1996) 115-130; or H. Bundgaard, Drugs of the Future 16 (1991) 443 which are all incorporated herein by reference. Suitable prodrugs for the compounds of the formula I are especially acyl prodrugs and carbamate prodrugs of acylatable nitrogen-containing groups such as amino groups and the guanidino group and also ester prodrugs and amide prodrugs of carboxylic acid groups which may be present in compounds of the formula I. In the acyl prodrugs and carbamate prodrugs one or more, for example one or two, hydrogen atoms on nitrogen atoms in such groups are replaced with an acyl group or a carbamate, preferably a  $-(C_1-C_6)$ -alkyloxycarbonyl group. Suitable acyl groups and carbamate groups for acyl prodrugs and carbamate prodrugs are, for example, the groups  $RP^1-CO-$  and  $RP^2O-CO-$ , in which  $RP^1$  is hydrogen,  $(C_1-C_{18})$ -alkyl,  $(C_3-C_8)$ -cycloalkyl,  $(C_3-C_8)$ -cycloalkyl- $(C_1-C_4)$ -alkyl-,  $(C_6-C_{14})$ -aryl, Het-,  $(C_6-C_{14})$ -aryl- $(C_1-C_4)$ -alkyl- or Het- $(C_1-C_4)$ -alkyl- and in which  $RP^2$  has the meanings indicated for  $RP^1$  with the exception of hydrogen.

**[0031]** Especially preferred compounds of the formula I are those wherein two or more residues are defined as indicated before for preferred compounds of the formula I, or residues can have one or some of the specific denotations of the residues given in their general definitions or in the definitions of preferred compounds before. All possible combinations of definitions given for preferred definitions and of specific denotations of residues explicitly are a subject of the present invention.

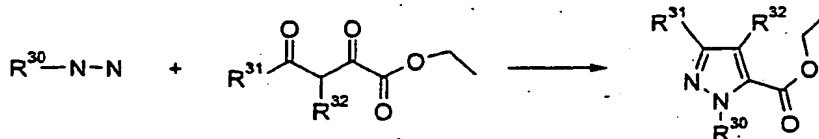
**[0032]** Also with respect to all preferred compounds of the formula I all their stereoisomeric forms and mixtures thereof in any ratio and their physiologically acceptable salts explicitly are a subject of the present invention, as well as are their prodrugs. Similarly, also in all preferred compounds of the formula I, all residues that are present more than one time in the molecule are independent of each other and can be identical or different.

**[0033]** The compounds of the formula I can be prepared by utilising procedures and techniques, which per se are well known and appreciated by one of ordinary skill in the art. Starting materials or building blocks for use in the general synthetic procedures that can be applied in the preparation of the compounds of formula I are readily available to one of ordinary skill in the art. In many cases they are commercially available or have been described in the literature. Otherwise they can be prepared from readily available precursor compounds analogously to procedures described in the literature, or by procedures or analogously to procedures described in this application.

**[0034]** In general, compounds of the formula I can be prepared, for example in the course of a convergent synthesis, by linking two or more fragments which can be derived retrosynthetically from the formula I. More specifically, suitably substituted starting Pyrazole derivatives are employed as building blocks in the preparation of the compounds of formula I. If not commercially available, such Pyrazole derivatives can be prepared according to the well-known standard procedures for the formation of the Pyrazole ring system. By choosing suitable precursor molecules, these pyrazole syntheses allow the introduction of a variety of substituents into the various positions of the pyrazole system, which can be chemically modified in order to finally arrive at the molecule of the formula I having the desired substituent pattern. As one of the comprehensive reviews in which numerous details and literature references on the chemistry of pyrazole and on synthetic procedures for their preparation can be found, J. Eiguero in "Comprehensive Heterocyclic Chemistry II"; Eds. A. Katritzky, Ch. Rees, E. Scriven; Elsevier 1996, Vol. 3; K. Kirschke in Houben-Weyl, "Methoden der Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Germany 1994, Vol. E8b Heteroarene; T. Nagai et al. Org. Prep. Proced. Int. (1993), 25, 403; M. Elnagdi et al. Heterocycles (1985) 23, 3121; K. Makino et al. J. Heterocycl. Chem. (1998) 35, 489; K. Makino et al. J. Heterocycl. Chem. (1999) 36, 321. If starting pyrazole derivatives are not commercially available and have to be synthesized this can be done, for example, according to the well-known pyrazole syntheses mentioned above. In the following procedures of particular interest for the embodiment of this invention are listed and referenced briefly, however, they are standard procedures comprehensively discussed in the literature, and are well known to one skilled in the art. Although not always shown explicitly, in certain cases positional isomers will occur during the synthesis of the below mentioned reactions. Nevertheless such mixtures of positional isomers, can be separated by modern separation techniques like, for example, preparative HPLC.

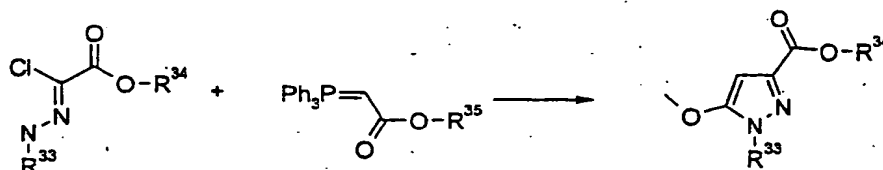
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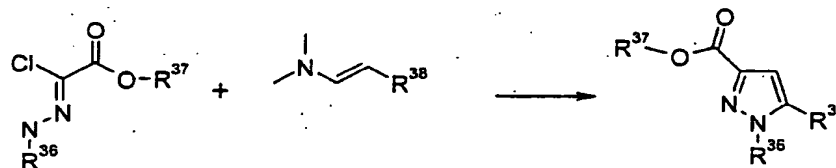


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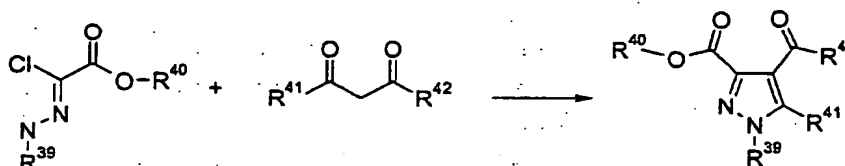
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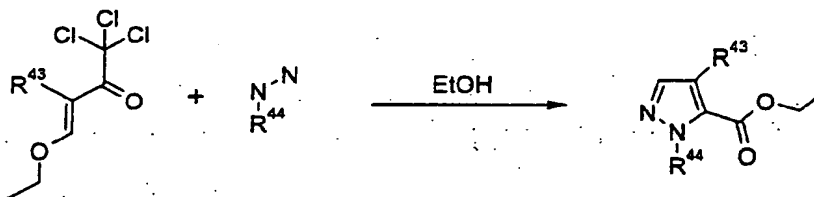


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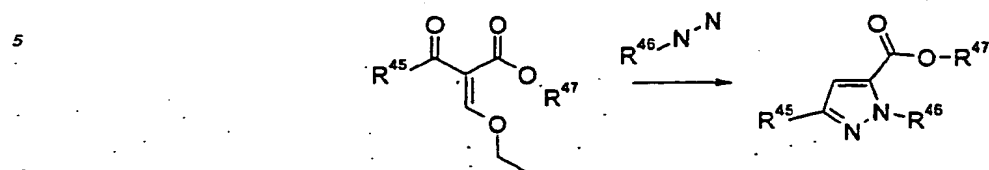


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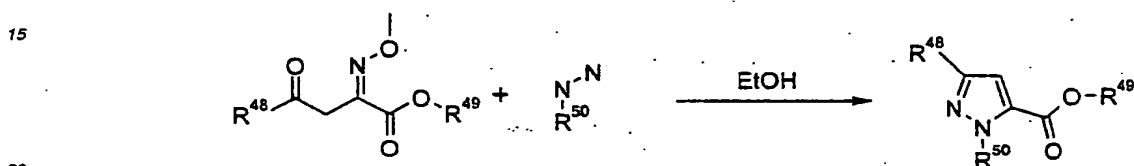
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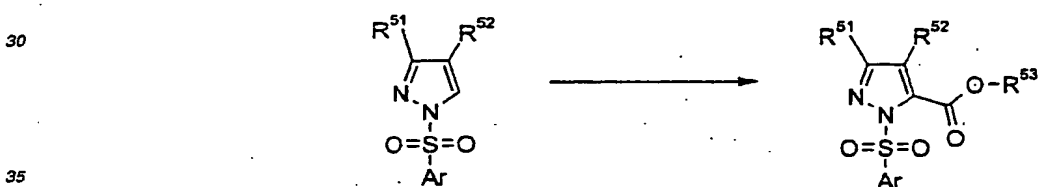


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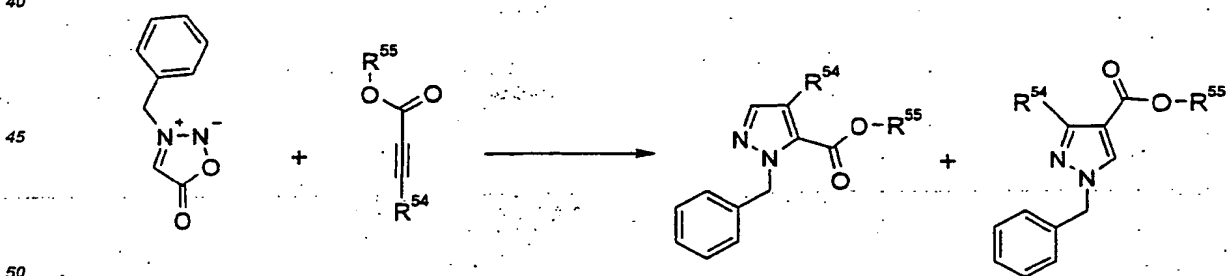


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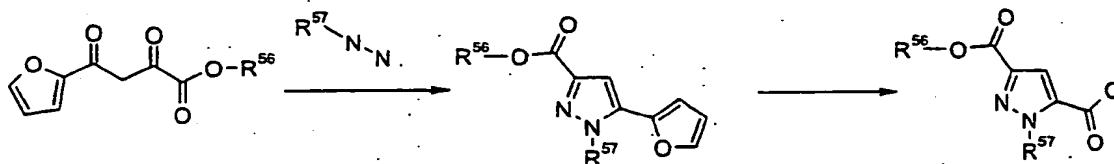
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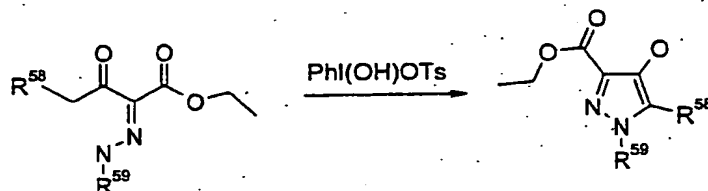
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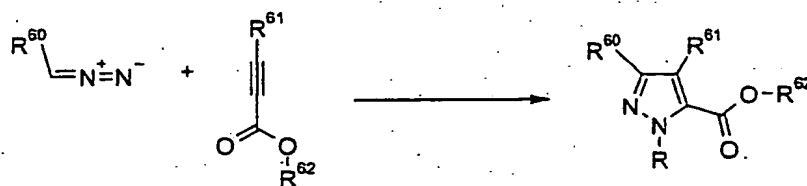




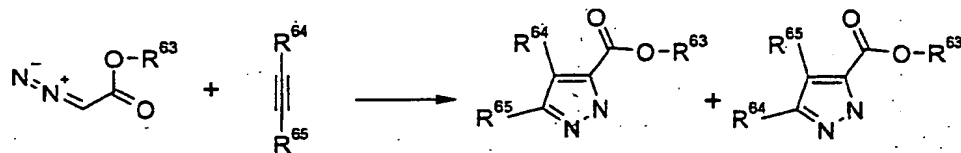
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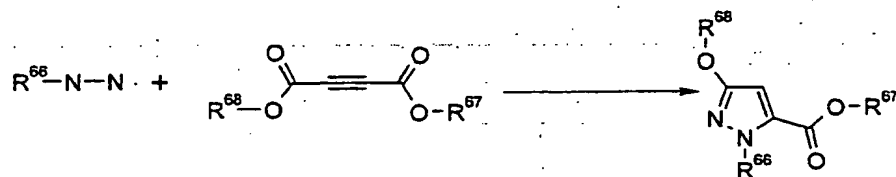
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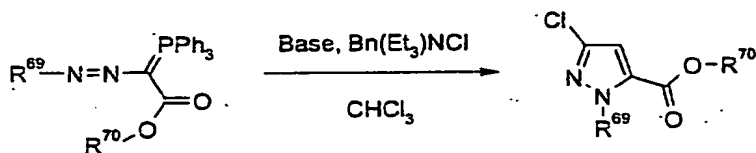
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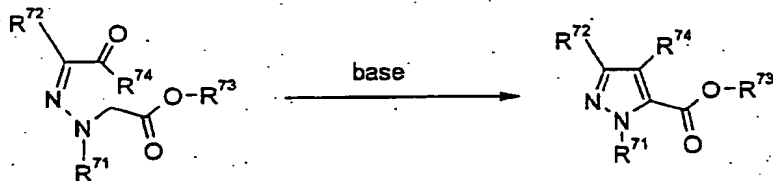
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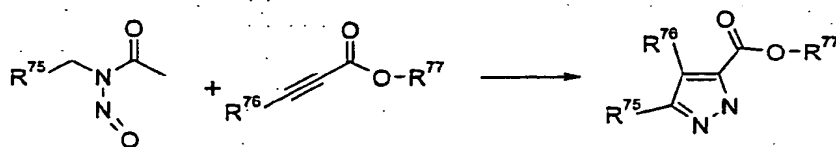
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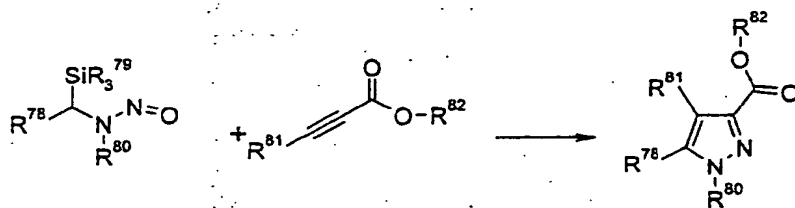
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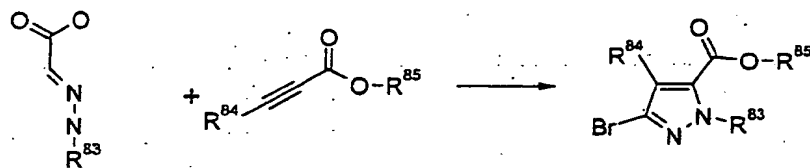
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[0035] Further, in order to obtain the desired substituents at the pyrazole ring system in the formula I, the functional groups introduced into the ring system during the pyrazole synthesis can be chemically modified. Especially the groups present in the pyrazole ring system can be modified by a variety of reactions and thus the desired residues  $R^{1a}$ ,  $R^{1b}$  be obtained. For example, a pyrazole carrying a hydrogen atom in the 3-position can also be obtained by saponification and subsequent decarboxylation of pyrazole carrying an ester group in the respective position. Alkyl- or hydroxymethyl groups as well as formyl groups attached to the pyrazole core can be transformed to a variety of functional groups, for

example, to the corresponding carboxylic acid or carboxylic ester by many oxidative reactions well known to those skilled in the art. Moreover a nitrile group attached to the pyrazole ring can, for example, easily be converted into the desired acid under acidic or basic conditions. In addition, carboxylic acid groups and acetic acid groups in the 3-position, the 4-position and the 5-position can be converted into their homologues by usual reactions for chain elongation of carboxylic acids. Halogen atoms can be introduced into the 3-position, the 4-position and the 5-position, for example according to procedures like the following described in the literature. For the fluorination of pyrazoles N-fluoro-2,4,6-trimethylpyridinium triflate is the reagent of choice (T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, K. Tomita, *J. Am. Chem. Soc.* (1990) 112, 8563 see also K. Manko et al., *J. Fluorine Chem.* (1988) 39, 435; R. Storer et al. *Nucleosides Nucleotides* (1999) 18; 203) however, other suitable fluorinating reagents may also be employed where appropriate. The chlorination, bromination, or iodination of pyrazoles can be accomplished by the reaction with elemental halogens or by the use of NCS, NBS or NIS and many other reagents well known to those skilled in the art. In addition suitable procedures are for example reported by M. Rodriguez-Franco et al., *Tetrahedron Lett.* (2001) 42, 863; J. Pawlas et al., *J. Org. Chem.* (2000) 65, 9001; Y. Huang et al., *Org Lett* (2000) 2, 2833; W. Holzer et al., *J. Heterocycl. Chem.* (1995) 32, 1351; N. Kudo et al., *Chem. Pharm. Bull.* (1999) 47, 857; G. Auzzi et al., *Farmaco, Ed Sci* (1979) 34, 743; K. Morimoto et al., *J. Heterocycl. Chem.* (1997) 34, 537; D. Jeon et al., *Synth. Commun.* (1998) 28, 2159. Depending on the reaction conditions, reagent, stoichiometry and substitution pattern the halogen is introduced in the 3-position and/or 4-position and/or 5-position. By selective halogen/metal exchange or metalation by selective hydrogen/metal exchange and subsequent reaction with a wide range of electrophiles various substituents can be introduced at the heterocyclic nucleus. (M. R. Grimmett, *Heterocycles* (1994) 37, 2087; V. D. Gardner et al., *J. Heterocycl. Chem.* (1984), 21, 121; D. Butler et al., *J. Org. Chem.* (1971) 36, 2542). Halogens or hydroxy groups (via their triflates or nonaflates) - or primary amines (via their diazonium salts) present in the pyrazole structure - can be converted directly, or after interconversion to the corresponding stannane, or boronic acid, into a variety of other functional groups like for example -CN, -CF<sub>3</sub>, -C<sub>2</sub>F<sub>5</sub>; ethers, acids, amides, amines, alkyl- or aryl- groups mediated by means of transition metals, namely palladium or nickel catalysts or copper salts and reagents for example referred to below (F. Diederich, P. Stang, *Metal-catalyzed Cross-coupling Reactions*, Wiley-VCH, 1998; or M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, Wiley-VCH, 1998; J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, 1996; J. Hartwig, *Angew. Chem.* (1998) 110, 2154; B. Yang, S. Buchwald, *J. Organomet. Chem.* (1999) 576, 125; T. Sakamoto, K. Ohsawa, *J. Chem. Soc. Perkin Trans I* (1999) 2323; D. Nichols, S. Frescas, D. Marona-Lewicka, X. Huang, B. Roth, G. Gudelsky, J. Nash, *J. Med. Chem.* (1994) 37, 4347; P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan, A. Combs, *Tetrahedron Lett.* (1998) 39, 2941; D. Chan, K. Monaco, R. Wang, M. Winters, *Tetrahedron Lett.* (1998) 39, 2933; V. Farina, V. Krishnamurthy, W. Scott, *The Stille Reaction*, Wiley, 1994; F. Qing et al. *J. Chem. Soc. Perkin Trans. I* (1997) 3053; S. Buchwald et al. *J. Am. Chem. Soc.* (2001) 123, 7727; S. Kang et al. *Synlett* (2002) 3, 427; S. Buchwald et al. *Organic Lett.* (2002) 4, 581; T. Fuchikami et al. *Tetrahedron Lett.* (1991) 32, 91; Q. Chen et al. *Tetrahedron Lett.* (1991) 32, 7689). For example, nitro groups can be reduced to amino groups by means of various reducing agents, such as sulfides, dithionites, complex hydrides or by catalytic hydrogenation. A reduction of a nitro group may also be carried out at a later stage of the synthesis of a compound of the formula I, and a reduction of a nitro group to an amino group may also occur simultaneously with a reaction performed on another functional group, for example when reacting a group like a cyano group with hydrogen sulfide or when hydrogenating a group. In order to introduce the residues R<sup>1a</sup>, R<sup>1b</sup>, amino groups can then be modified according to standard procedures for alkylation, for example by reaction with (substituted) alkyl halogenides or by reductive amination of carbonyl compounds, according to standard procedures for acylation, for example by reaction with activated carboxylic acid derivatives such as acid chlorides, anhydrides, activated esters or others or by reaction with carboxylic acids in the presence of an activating agent, or according to standard procedures for sulfonylation, for example by reaction with sulfonyl chlorides.

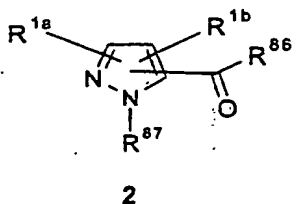
**[0036]** Ester groups present in the pyrazole nucleus can be hydrolyzed to the corresponding carboxylic acids, which after activation can then be reacted with amines or alcohols under standard conditions to give amides or alcohols, respectively. Ester groups present in the pyrazole nucleus can be converted to other esters by transesterification. Carboxylic acids attached to a suitable pyrazole nucleus can also be alkylated to give esters. Ether groups present at the pyrazole nucleus, for example benzyloxy groups or other easily cleavable ether groups, can be cleaved to give hydroxy groups which then can be reacted with a variety of agents, for example etherification agents or activating agents allowing replacement of the hydroxy group by other groups. Sulfur-containing groups can be reacted analogously.

**[0037]** During the course of the synthesis in order to modify the groups R<sup>87</sup> or R<sup>8'</sup> attached to the pyrazole ring system by application of parallel synthesis methodology, a variety of reactions can be extremely useful, including, for example, palladium, nickel or copper catalysis. Such reactions are described for example in F. Diederich, P. Stang, *Metal-catalyzed Cross-coupling Reactions*, Wiley-VCH (1998); or M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, Wiley-VCH (1998); J. Tsuji, *Palladium Reagents and Catalysts*, Wiley (1996); J. Hartwig, *Angew. Chem.* (1998) 110, 2154; B. Yang, S. Buchwald, *J. Organomet. Chem.* (1999), 576, 125; P. Lam, C. Clark, S. Saubern, J. Adams, M. Winters, D. Chan, A. Combs, *Tetrahedron Lett.* (1998) 39, 2941; D. Chan, K. Monaco, R. Wang, M. Winters, *Tetrahedron Lett.*

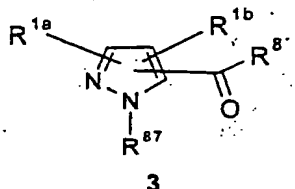
(1998) , 39, 2933; J. Wolfe, H. Tomori, J. Sadighi, J. Yin, S. Buchwald, J. Org. Chem. (2000) , 65, 1158; V. Farina, V. Krishnamurthy, W. Scott, The Stille Reaction, Wiley, (1994); S. Buchwald et al., J. Am. Chem. Soc. (2001) , 123, 7727; S. Kang et al., Synlett (2002) , 3, 427; S. Buchwald et al., Org. Lett. (2002), 4, 581.

[0038] The previously-mentioned reactions for the conversion of functional groups are furthermore, in general, extensively described in textbooks of organic chemistry like M. Smith, J. March, March's Advanced Organic Chemistry, Wiley-VCH, 2001 and in treatises like Houben-Weyl, "Methoden der Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Germany, or "Organic Reactions", John Wiley & Sons, New York, or R. C. Larock, "Comprehensive Organic Transformations", Wiley-VCH, 2<sup>nd</sup> ed (1999), B. Trost, I. Fleming (eds.) Comprehensive Organic Synthesis, Pergamon, 1991; A. Katritzky, C. Rees, E. Scriven. Comprehensive Heterocyclic Chemistry II, Elsevier Science, 1996) in which details on the reactions and primary source literature can be found. Due to the fact that in the present case the functional groups are attached to a pyrazole ring it may in certain cases become necessary to specifically adapt reaction conditions or to choose specific reagents from a variety of reagents that can in principle be employed into a conversion reaction, or otherwise to take specific measures for achieving a desired conversion, for example to use protection group techniques. However, finding out suitable reaction variants and reaction conditions in such cases does not cause any problems for one skilled in the art. The structural elements present in the residues attached at the 1-position of the pyrazole ring in the compounds of the formula I and in the COR<sup>8'</sup> group present in the 3-position and/or in the 5-position of the pyrazole ring can be introduced into the starting pyrazole derivative obtainable as outlined above by consecutive reaction steps using synthesis methodologies like those outlined below using procedures which per se are well known to one skilled in the art.

[0039] The residues R<sup>8'</sup> that can be introduced in formula 2, for example, by condensing a corresponding carboxylic acid of the formula 2 with a compound of the formula HR<sup>8'</sup>, i. e. with an amine of the formula HN(R<sup>1'</sup>)R<sup>2'-V-G-M</sup> to give a compound of the formula 3. The compound of the formula 3 thus obtained can already contain the desired final groups, i. e. the groups R<sup>8'</sup> and R<sup>87</sup> can be the groups -N(R<sup>1'</sup>)-R<sup>2'-V-G-M</sup> and R<sup>0-Q-</sup> as defined in the formula I, or optionally in the compound of the formula 3 thus obtained subsequently the residue or the residues R<sup>8'</sup> and the residue R<sup>87</sup> are converted into the residues -N(R<sup>1'</sup>)R<sup>2'-V-G-M</sup> and R<sup>0-Q-</sup>, respectively, to give the desired compound of the formula I.



HR<sup>8'</sup>



formula I

[0040] Thus, the residues R<sup>8'</sup> and the residues R<sup>1'</sup> and R<sup>2'-V-G-M</sup> contained therein can have the denotations of R<sup>1</sup> and R<sup>2-V-G-M</sup>, respectively, given above or in addition in the residues R<sup>1'</sup> and R<sup>2'-V-G-M</sup> functional groups can also be present in the form of groups that can subsequently be transformed into the final groups R<sup>1</sup> and R<sup>2-V-G-M</sup>, i.e. functional groups can be present in the form of precursor groups or of derivatives, for example in protected form. In the course of the preparation of the compounds of the formula I it can generally be advantageous or necessary to introduce functional groups which reduce or prevent undesired reactions or side reactions in the respective synthesis step, in the form of precursor groups which are later converted into the desired functional groups, or to temporarily block functional groups by a protective group strategy suited to the synthesis problem. Such strategies are well known to those skilled in the art (see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, Wiley, 1991, or P. Kocienski, Protecting Groups, Thieme 1994). As examples of precursor groups nitro groups and cyano groups may be mentioned which can in a later step be transformed into carboxylic acid derivatives or by reduction into ami-

nomethyl groups, or nitro groups which may be transformed by reduction, for example catalytic hydrogenation into amino groups by reduction. Protective groups can also have the meaning of a solid phase, and cleavage from the solid phase stands for the removal of the protective group. The use of such techniques is known to those skilled in the art (Burgess K (Ed.) Solid Phase Organic Synthesis, New York, Wiley, 2000). For example, a phenolic hydroxy group can be attached to a trityl-polystyrene resin, which serves as a protecting group, and the molecule is cleaved from this resin by treatment with TFA at a later stage of the synthesis.

[0041] The residue  $R^{87}$  in the compounds of the formulae 2 and 3 can denote the group  $-Q-R^0$  as defined above which finally is to be present in the desired target molecule of the formula I, or it can denote a group which can subsequently be transformed into the group  $-Q-R^0$ , for example a precursor group or a derivative of the group  $-Q-R^0$  in which functional groups are present in protected form, or  $R^{87}$  can denote a hydrogen atom or a protective group for the nitrogen atom of the pyrazole ring. Similarly, the residues  $R^{1a}$  and  $R^{1b}$  in the formulae 2 and 3 have the corresponding definitions of  $R^4$  and  $R^3$  in formula I as defined above, however, for the synthesis of the compounds of the formula I these residues, too, can in principle be present at the stage of the condensation of a compound of the formula 2 with a compound of the formula  $HR^{87}$  giving a compound of the formula 3 in the form of precursor groups or in protected form.

[0042] The residues  $R^{86}$  in the compounds of the formula 2 which can be identical or different, can be, for example, hydroxy or  $(C_1-C_4)$ -alkoxy, i. e., the groups  $COR^{86}$  present in the compounds of the formula 2 can be, for example, the free carboxylic acids or esters thereof like alkyl esters as can be the groups  $COR^{87}$  in the compounds of the formula I. The groups  $COR^{86}$  can also be any other activated derivative of a carboxylic acid which allows amide formation, ester formation or thioester formation with a compound of the formula  $HR^{87}$ . The group  $COR^{86}$  can be, for example, an acid chloride, an activated ester like a substituted phenyl ester or an N-hydroxysuccinimide or a hydroxybenzotriazole ester, an azolide like an imidazolide, an azide or a mixed anhydride, for example a mixed anhydride with a carbonic acid ester or with a sulfonic acid, which derivatives can all be prepared from the carboxylic acid by standard procedures and can be reacted with an amine, an alcohol or a mercaptan of the formula  $HR^{87}$  under standard conditions. A carboxylic acid group  $COOH$  representing  $COR^{86}$  in a compound of the formula 2 can be obtained, for example, from an ester group introduced into the pyrazole system during a pyrazole synthesis by standard hydrolysis procedures. It can also be obtained, for example, by hydrolysis of a nitrile group introduced into the pyrazole system during a pyrazole synthesis.

[0043] Compounds of the formula I in which a group  $COR^{87}$  is an ester group can also be prepared from compounds of the formula 2 in which  $COR^{86}$  is a carboxylic acid group by common esterification reactions like, for example, reacting the acid with an alcohol under acid catalysis, or alkylation of a salt of the carboxylic acid with an electrophile like an alkyl halogenide, or by transesterification from another ester. Compounds of the formula I in which a group  $COR^{87}$  is an amide group can be prepared from amines and compounds of the formula 2 in which  $COR^{86}$  is a carboxylic acid group or an ester thereof by common amination reactions. Especially for the preparation of amides the compounds of the formula 2 in which  $COR^{86}$  is a carboxylic acid group can be condensed under standard conditions with compounds of the formula  $HR^{87}$  which are amines by means of common coupling reagents used in peptide synthesis. Such coupling reagents are, for example, carbodiimides like dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide, carbonyldi-azoles like carbonyldiimidazole (CDI) and similar reagents, propylphosphonic anhydride, O-((cyano-(ethoxycarbonyl)-methylene)amino)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TUTU), diethylphosphoryl cyanide (DEPC) or bis-(2-oxo-3-oxazolidinyl)-phosphoryl chloride (BOP-Cl) and many others.

[0044] If the residue  $-Q-R^0$  present in a pyrazole of the formula I or the residue  $R^{87}$  present in a pyrazole of the formula 2, or a residue in which functional groups within the residue  $-Q-R^0$  or  $R^{87}$  are present in protected form or in the form of a precursor group, have not already been introduced during a preceding step, for example during a synthesis of the pyrazole nucleus, these residues can, for example, be introduced into the 1-position of the pyrazole system by conventional literature procedures well known to one skilled in the art for N-alkylation, reductive amination, N-arylation, N-acylation or N-sulfonylation of ring nitrogen atoms of heterocycles. The starting pyrazole derivative that is to be employed in such a reaction carries a hydrogen atom in the 1-position. N-Alkylation of a ring nitrogen atom can, for example, be performed under standard conditions, preferably in the presence of a base like  $K_2CO_3$ ,  $Cs_2CO_3$ , NaH or  $KOtBu$ , using an alkylating compound of the formula  $LG-Q-R^0$  or of the formula  $R^{87}-LG$ , wherein the atom in the group Q or in the group  $R^{87}$  bonded to the group LG in this case is an aliphatic carbon atom of an alkyl moiety and LG is a leaving group, for example halogen like chlorine, bromine or iodine, or a sulfonyloxy group like tosyloxy, mesyloxy or trifluoromethylsulfonyloxy. LG may, for example, also be a hydroxy group which, in order to achieve the alkylation reaction, is activated in a well-known Mitsunobu reaction by a conventional activating agent. The regioselectivity of the N-alkylation can be controlled by the choice of the base, solvent and reaction conditions. Nevertheless mixtures of positional isomers, can be separated by modern separation techniques like, for example, flash chromatography, crystallisation or preparative HPLC.

[0045] For the preparation of compounds in which A is a direct linkage and an aromatic group is directly bonded to the 1-position of the pyrazole system, conventional arylation procedures can be used. For example aryl fluorides like alkyl fluorobenzoates or 4-fluorophenyl nitriles can be employed as arylating agents. Such processes are described,

for example, by K. Cooper et al., *J. Med. Chem.* (1992), 35, 3115; M. Artico et al., *Eur. J. Med. Chem. Chim. Ther.* (1992) 27, 219; X.-J. Wang et al., *Tetrahedron Letters* (2000) 41, 5321; M. L. Cerrada et al., *Synth. Commun.* (1993) 23, 1947. Alternatively a wide variety of substituted aryl iodides, aryl bromides or aryl triflates can serve as arylating agents at the 1-position of the heterocyclic nitrogen in a copper salt or palladium mediated reaction according for example to P. Cozzi et al. *Farmaco* (1987) 42, 205; P. Unangst, D. Connor, R. Stabler, R. Welkert, J. *Heterocycl. Chem.* (1987) 24, 811; G. Tokmakov, I. Grandberg, *Tetrahedron* (1995) 51, 2091; D. Old, M. Harris, S. Buchwald, *Org. Lett.* (2000) 2, 1403; G. Mann, J. Hartwig, M. Driver, C. Fernandez-Rivas, *J. Am. Chem. Soc.* (1998) 120, 827; J. Hartwig, M. Kawat-sura, S. Hauk, K. Shaughnessy, L. J. *Org. Chem.* (1999) 64, 5575; S. Buchwald et al., *J. Am. Chem. Soc.* (2001) 123, 7727. Moreover such arylations can also be accomplished by reaction of a wide range of substituted aryl boronic acids as demonstrated for example by P. Lam et al., *Tetrahedron Lett.* (1998) 39, 2941; V. Collot et al., *Tetrahedron Lett.* (2000) 41, 9053; P. Lam et al., *Tetrahedron Lett.* (2001) 42, 3415;

[0046] Preferred methods include, but are not limited to those described in the examples.

[0047] The compounds of the present invention are serine protease inhibitors, which inhibit the activity of the blood coagulation enzyme factors Xa and/or factor VIIa. In particular, they are highly active inhibitors of factor Xa. They are specific serine protease inhibitors inasmuch as they do not substantially inhibit the activity of other proteases whose inhibition is not desired. The activity of the compounds of the formula I can be determined, for example, in the assays described below or in other assays known to those skilled in the art. With respect to factor Xa inhibition, a preferred embodiment of the invention comprises compounds which have a  $K_i \leq 1$  mM for factor Xa inhibition as determined in the assay described below, with or without concomitant factor VIIa inhibition, and which preferably do not substantially inhibit the activity of other proteases involved in coagulation and fibrinolysis whose inhibition is not desired (using the same concentration of the inhibitor). The compounds of the invention inhibit factor Xa catalytic activity either directly, within the prothrombinase complex or as a soluble subunit, or indirectly, by inhibiting the assembly of factor Xa into the prothrombinase complex.

[0048] The present invention also relates to the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for use as pharmaceuticals (or medicaments), to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation, inflammatory response or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for the production of pharmaceuticals for the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses. The invention also relates to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for use in the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses, and to methods of treatment aiming at such purposes including methods for said therapies and prophylaxis. The present invention also relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an effective amount of at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs in addition to a customary pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable carrier substances or excipients and/or auxiliary substances or additives.

[0049] The invention also relates to the treatment of disease states such as abnormal thrombus formation, acute myocardial infarction, unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy or percutaneous transluminal coronary angioplasty, transient ischemic attacks, stroke, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, a risk of pulmonary thromboembolism, or disseminated systemic intravascular coagulopathy occurring in vascular systems during septic shock, certain viral infections or cancer.

[0050] The compounds of the formula I and their physiologically tolerable salts and their prodrugs can be administered to animals, preferably to mammals, and in particular to humans as pharmaceuticals for therapy or prophylaxis. They can be administered on their own, or in mixtures with one another or in the form of pharmaceutical preparations, which permit enteral or parenteral administration.

[0051] The pharmaceuticals can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatin capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or percutaneously or topically, for example in the form of ointments, solutions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art, pharmaceutically acceptable inert inorganic and/or organic carriers being used in addition to the compound(s) of the formula I and/or its (their) physiologically tolerable salts and/or its (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, cornstarch or derivatives thereof, talc, stearic acid or its salts, etc. Carriers for soft gelatin capsules and suppositories are, for example,

fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carriers for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, saline, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. The pharmaceutical preparations normally contain about 0.5 % to 90 % by weight of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. The amount of the active ingredient of the formula I and/or its physiologically tolerable salts and/or its prodrugs in the pharmaceutical preparations normally is from about 0.5 mg to about 1000 mg, preferably from about 1 mg to about 500 mg.

**[0052]** In addition to the active ingredients of the formula I and/or their physiologically acceptable salts and/or prodrugs and to carrier substances, the pharmaceutical preparations can contain additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. In case a pharmaceutical preparation contains two or more compounds of the formula I the selection of the individual compounds can aim at a specific overall pharmacological profile of the pharmaceutical preparation. For example, a highly potent compound with a shorter duration of action may be combined with a long-acting compound of lower potency. The flexibility permitted with respect to the choice of substituents in the compounds of the formula I allows a great deal of control over the biological and physico-chemical properties of the compounds and thus allows the selection of such desired compounds. Furthermore, in addition to at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

**[0053]** As inhibitors of factor Xa and/or factor VIIa the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for the therapy and prophylaxis of conditions in which the activity of factor Xa and/or factor VIIa plays a role or has an undesired extent, or which can favorably be influenced by inhibiting factor Xa and/or factor VIIa or decreasing their activities, or for the prevention, alleviation or cure of which an inhibition of factor Xa and/or factor VIIa or a decrease in their activity is desired by the physician. As inhibition of factor Xa and/or factor VIIa influences blood coagulation and fibrinolysis, the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for reducing blood clotting, or for the therapy and prophylaxis of conditions in which the activity of the blood coagulation system plays a role or has an undesired extent, or which can favorably be influenced by reducing blood clotting, or for the prevention, alleviation or cure of which a decreased activity of the blood coagulation system is desired by the physician. A specific subject of the present invention thus are the reduction or inhibition of unwanted blood clotting, in particular in an individual, by administering an effective amount of a compound I or a physiologically tolerable salt or a prodrug thereof, as well as pharmaceutical preparations therefor.

**[0054]** Conditions in which compounds of the formula I can be favorably used include, for example, cardiovascular disorders, thromboembolic diseases or complications associated, for example, with infection or surgery. The compounds of the present invention can also be used to reduce an inflammatory response. Examples of specific disorders for the treatment or prophylaxis of which the compounds of the formula I can be used are coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure, stroke and disseminated intravascular clotting disorder. Examples of related complications associated with surgery are thromboses like deep vein and proximal vein thrombosis, which can occur following surgery. In view of their pharmacological activity the compounds of the invention can replace or supplement other anticoagulant agents such as heparin. The use of a compound of the invention can result, for example, in a cost saving as compared to other anticoagulants. When using the compounds of the formula the dose can vary within wide limits and, as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease to be treated, on the mode and the schedule of administration, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. An appropriate dosage can be established using clinical approaches well known in the medical art. In general, the daily dose for achieving the desired results in an adult weighing about 75 kg is from 0.01 mg/kg to 100 mg/kg, preferably from 0.1 mg/kg to 50 mg/kg, in particular from 0.1 mg/kg to 10 mg/kg, (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts, into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it may be necessary to deviate upwards or downwards from the daily dose indicated.

**[0055]** A compound of the formula I can also advantageously be used as an anticoagulant outside an individual. For example, an effective amount of a compound of the invention can be contacted with a freshly drawn blood sample to prevent coagulation of the blood sample. Further, a compound of the formula I and its salts can be used for diagnostic purposes, for example in *in vitro* diagnoses, and as an auxiliary in biochemical investigations. For example, a compound of the formula I can be used in an assay to identify the presence of factor Xa and/or factor VIIa or to isolate factor Xa and/or factor VIIa in a substantially purified form. A compound of the invention can be labeled with, for example, a

radioisotope, and the labeled compound bound to factor Xa and/or factor VIIa is then detected using a routine method useful for detecting the particular label. Thus, a compound of the formula I or a salt thereof can be used as a probe to detect the location or amount of factor Xa and/or factor VIIa activity in vivo, in vitro or ex vivo.

[0056] Furthermore, the compounds of the formula I can be used as synthesis intermediates for the preparation of other compounds, in particular of other pharmaceutical active ingredients, which are obtainable from the compounds of the formula I, for example by introduction of substituents or modification of functional groups.

[0057] The general synthetic sequences for preparing the compounds useful in the present invention are outlined in the examples given below. Both an explanation of, and the actual procedure for, the various aspects of the present invention are described where appropriate. The following examples are intended to be merely illustrative of the present invention, and not limiting thereof in either scope or spirit. Those with skill in the art will readily understand that known variations of the conditions and processes described in the examples can be used to synthesize the compounds of the present invention.

[0058] It is understood that changes that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Thus, the following examples are intended to illustrate but not limit the present invention.

#### Examples

[0059] When in the final step of the synthesis of a compound an acid such as trifluoroacetic acid or acetic acid was used, for example when trifluoroacetic acid was employed to remove a tBu group or when a compound was purified by chromatography using an eluent which contained such an acid, in some cases, depending on the work-up procedure, for example the details of a freeze-drying process, the compound was obtained partially or completely in the form of a salt of the acid used, for example in the form of the acetic acid salt or trifluoroacetic acid salt or hydrochloric acid salt.

[0060] Abbreviations used:

tert-Butyl	tBu
2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	Binap
Bis-(oxo-3-oxazolidinyl)-phosphoryl chloride	BOP-Cl
dibenzylidenacetone	dba
Dichloromethane	DCM
Dicyclohexyl-carbodiimide	DCC
Diethylphosphoryl cyanide	DEPC
4-Dimethylaminopyridine	DMAP
N,N-Dimethylformamide	DMF
Dimethylsulfoxide	DMSO
1,1'-Bis(diphenylphosphino)ferrocene	DPPF
O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate	HATU
N-Bromosuccinimide	NBS
N-Chlorosuccinimide	NCS
N-Iodosuccinimide	NIS
N-Ethylmorpholine	NEM
Methanol	MeOH
Room temperature 20 °C to 25 °C	RT
Saturated	sat.
Tetrahydrofuran	THF
Trifluoroacetic acid	TFA
O-((Ethoxycarbonyl)cyanomethyleneamino)-N,N,N',N'-tetramethyluronium	
tetrafluoroborate	TOTU

Example 1: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) (1-Isopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester

[0061] To a solution of 5.0 g Piperidin-4-yl-carbamic acid tert-butyl ester in 15 ml methanol 7.34 ml acetone, 3.14 g Na(CN)BH<sub>3</sub> and 0.3 ml acetic acid were added. After stirring for 16 h at RT the solvent was removed under reduced



pressure and the residue was partitioned between 30 ml of water and 30 ml of ethyl acetate. The organic layer was washed with saturated  $\text{Na}_2\text{CO}_3$  solution, water and then dried over  $\text{Na}_2\text{SO}_4$ . Following filtration, the solvent was removed under reduced pressure to yields a white solid.

5 Yield: 4.8g MS (ES<sup>+</sup>): m/e= 243.

(ii) 1-Isopropyl-piperidin-4-ylamine

10 **[0062]** To 4.8 g (1-Isopropyl-piperidin-4-yl)-carbamic acid tert-butyl ester in 15 ml methanol, 20 ml methanolic hydrochloric acid (8M) were added and the mixture was stirred for 16 h. Removal of the solvent under reduced pressure yielded a white solid, which was coevaporated twice with 20 ml toluene. The product was obtained as its hydrochloride.

Yield: 5.42 g MS (ES<sup>+</sup>): m/e= 143.

15 (iv) 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester

20 **[0063]** To a solution of 2.0 g 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester in 5 ml DMF, 360 mg NaH (60% in oil) and subsequently 2.8 g 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole [prepared by adopting a procedure described by Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Aiwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B; PCT Int. Appl. (2001) 460 pp. WO 0107436 A2] were added and the mixture was stirred at 80 °C for 1h. After the addition of 5 ml water the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. The residue was directly subjected to the subsequent saponification reaction without further purification.

25 Yield: 4 g.

(v) 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid

30 **[0064]** To a solution of 4 g 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester in 20 ml THF, 10 ml water and 500 mg lithium hydroxide monohydrate were added. After stirring for 2 h at 60°C the reaction was cooled to RT. The mixture was acidified with half concentrated hydrochloric acid to pH 3 and the precipitate collected by filtration and washed with 10-ml water. The product was obtained as a white solid which was dried under reduced pressure.

Yield: 3.8g.

35 (vi) 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

40 **[0065]** To a solution of 200 mg 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid, 0.3 ml N-NEM in 2 ml DCM, 168 mg TOTU were added and the mixture was stirred for 30 min at RT. Then 136 mg 1-Isopropyl-piperidin-4-ylamine hydrochloride were added and the reaction was further stirred for 2 h. After the addition of 2 ml sat.  $\text{NaHCO}_3$  the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. The residue was purified by preparative HPLC (C18 reverse phase column, elution with a  $\text{H}_2\text{O}/\text{MeCN}$  gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

45 Yield: 120 mg MS (ES<sup>+</sup>): m/e = 516, chloro pattern.

50 Example 2: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0066]** This compound was isolated as a by-product in example 1.  
MS (ES<sup>+</sup>): m/e = 516, chloro pattern.

55 Example 3: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0067]** The title compound was prepared analogously to example 1 with the difference that 5-Methyl-2H-pyrazole-

3-carboxylic acid methyl ester was used instead of 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester.  
MS (ESI<sup>+</sup>): m/e = 448, chloro pattern.

Example 4: 2-(6-Chloro-benzothiazol-2-yl)-5-methyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0068]** The title compound was prepared analogously to example 1 with the difference that 2-(6-Chloro-benzothiazol-2-yl)-5-methyl-2H-pyrazole-3-carboxylic acid was used instead of 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester.

MS (ESI<sup>+</sup>): m/e = 418, chloro pattern.

Example 5: 5-(5-Chloro-thiophen-2-yl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0069]** The title compound was prepared analogously to example 1 with the difference that 5-(5-Chloro-thiophen-2-yl)-2H-pyrazole-3-carboxylic acid methyl ester was used instead of 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester.

MS (ESI<sup>+</sup>): m/e = 550, chloro pattern.

Example 6: 5-(5-Chloro-thiophen-2-yl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0070]** This compound was isolated as a by-product in example 5.

MS (ES<sup>+</sup>): m/e = 550, chloro pattern.

Example 7: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(2,4-dichloro-phenyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0071]** The title compound was prepared analogously to example 1 with the difference that 4-(2,4-Dichloro-phenyl)-2H-pyrazole-3-carboxylic acid methyl ester was used instead of 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester.

MS (ESI<sup>+</sup>): m/e = 578, chloro pattern.

Example 8: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-propyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0072]** The title compound was prepared analogously to example 1 with the difference that 5-Propyl-2H-pyrazole-3-carboxylic acid methyl ester was used instead of 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester.

MS (ESI<sup>+</sup>): m/e = 476, chloro pattern.

Example 9: 5-tert-Butyl-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0073]** The title compound was prepared analogously to example 1 with the difference that 5-tert-Butyl-2H-pyrazole-3-carboxylic acid methyl ester was used instead of 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester.

MS (ESI<sup>+</sup>): m/e 490, chloro pattern.

Example 10: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-propyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

(i) 4-Iodo-5-propyl-2H-pyrazole-3-carboxylic acid ethyl ester

**[0074]** 1.0 g (5.5 mmol) of 5-propyl-2H-pyrazole-3-carboxylic acid ethyl ester was dissolved in 15 ml of dichloromethane and 1.23 g (5.5 mmol) of N-iodosuccinimide was added. The resulting solution was stirred at room temperature for 16 h. The solution was washed with aqueous sodium thiosulfate solution. The organic phase was dried with sodium sulfate and filtered. The resulting solution was passed through a short silica gel column, washing with dichloromethane. The solvent was removed under reduced pressure.

Yield: 1.5 g MS (LCMS-ES<sup>+</sup>): m/e = 309.

## (ii) 4-Cyano-5-propyl-2H-pyrazole-3-carboxylic acid ethyl ester

[0075] 1.5 g (4.9 mmol) of 4-Iodo-5-propyl-2H-pyrazole-3-carboxylic acid ethyl ester, 0.87 g (9.7 mmol) of copper cyanide and 404 mg (2.4 mmol) of tetraethylammonium cyanide were dissolved in 10 ml of DMF and 20 ml of tetrahydrofuran and the solution was degassed with argon. 223 mg (0.2 mmol) of Tris(dibenzylideneacetone)dipalladium (0) and 404 mg (0.7 mmol) of 1,1'-bis-(diphenylphosphino) ferrocene were added at RT. The reaction was stirred at 120°C for 5 h. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and this solution was washed with saturated aqueous sodium bicarbonate. The organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The product was purified by silica gel chromatography eluting with n-heptane:ethyl acetate/1:1.

Yield: 110 mg MS (LCMS-ES<sup>+</sup>): m/e = 208.

[0076] (iii) 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-propyl-2H-pyrazole-3-carboxylic acid 112 mg (0.5 mmol) of 4-cyano-5-propyl-2H-pyrazole-3-carboxylic acid ethyl ester was dissolved in 2 ml of DMF and 23.8 mg (0.6 mmol) of sodium hydride (60% in oil) were added at RT. After stirring for 20 min at room temperature the solution was cooled to -70°C and 166 mg (0.6 mmol) of 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added. The reaction was stirred at room temperature for 3 h. The reaction solution was treated with 1 ml of 2N aqueous NaOH for 16h at room temperature. The product was purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). After lyophilization the product was obtained as a white solid. Yield 55.3 mg. MS (LCMS-ES<sup>+</sup>): m/e = 377, chloro pattern.

(iv) 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-propyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0077] To a solution of 55 mg 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-propyl-2H-pyrazole-3-carboxylic acid, 0.1 ml N-NEM in 2 ml DMF, 48 mg TOTU were added and the mixture was stirred for 30 min at RT. Then 31 mg of 1-Isopropyl-piperidin-4-ylamine hydrochloride were added and the reaction was further stirred for 2 h. After addition of 2 ml sat. NaHCO<sub>3</sub> the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H<sub>2</sub>O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 18 mg MS (ES<sup>+</sup>): m/e = 501, chloro pattern.

Example 11: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-propyl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0078] This compound was isolated as a by-product in example 10. MS (ES<sup>+</sup>): m/e = 501, chloro pattern.

Example 12: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

## (i) 4-Iodo-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester

[0079] 1.0 g (4.5 mmol) of 5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester was dissolved in 15 ml of dichloromethane and 1.01 g (4.5 mmol) of N-iodosuccinimide was added. The resulting solution was stirred at room temperature for 16 h. The solution was washed with aqueous sodium thiosulfate solution. The organic phase was dried with sodium sulfate and filtered. The resulting solution was passed through a short silica gel column, washing with dichloromethane. The solvent was removed under reduced pressure.

Yield: 1.57 g MS (LCMS-ES<sup>+</sup>): m/e = 349.

## (ii) 4-Cyano-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester

[0080] 1.57 g (4.5 mmol) of 4-Iodo-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester, 0.81 g (9.0 mmol) of

copper cyanide and 352 mg (2.3 mmol) of tetraethylammonium cyanide were dissolved in 10 ml of DMF and 20 ml of tetrahydrofuran and the solution was degassed with argon. 223 mg (0.2 mmol) of Tris(dibenzylideneacetone)dipalladium (0) and 374 mg (0.7 mmol) of 1,1'-bis-(diphenylphosphino) ferrocene were added at RT. The reaction was stirred at 120°C for 5 h. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and this solution was washed with saturated aqueous sodium bicarbonate. The organic phase was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The product was purified by silica gel chromatography eluting with n-heptane:ethyl acetate/1:1.

Yield: 287 mg MS (LCMS-ES<sup>+</sup>): m/e = 248.

(iii) 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid

**[0081]** 287 mg (1.2 mmol) of 4-Cyano-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester was dissolved in 2 ml of DMF and 51.1 mg (1.3 mmol) of sodium hydride (60% in oil) were added at RT. After stirring for 20 min at room temperature the solution was cooled to -70°C and 355 mg (1.3 mmol) of 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added. The reaction was stirred at room temperature for 3 h. The reaction solution was treated with 1 ml of 2N aqueous NaOH for 16h at room temperature. The product was purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). After lyophilization the product was obtained as a white solid.

Yield 122 mg. MS (LCMS-ES<sup>+</sup>): m/e = 417.

(iv) 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0082]** To a solution of 31 mg 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid, 0.1 ml N-NEM in 1 ml DMF, 24 mg TOTU were added and the mixture was stirred for 30 min at RT. Then 16 mg 1-Isopropyl-piperidin-4-ylamine hydrochloride were added and the reaction was further stirred for 2 h. After addition of 2 ml sat. NaHCO<sub>3</sub> the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a H<sub>2</sub>O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 18 mg MS (ES<sup>+</sup>): m/e = 541, chloro pattern.

Example 13: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0083]** This compound was isolated as a by-product in example 12.  
MS (ES<sup>+</sup>): m/e = 541, chloro pattern.

Example 14: 2-[2-(5-Chloro-thiophen-2-yl)-thiazol-4-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0084]** The title compound was prepared analogously to example 1 with the difference that 5-Bromomethyl-2-(5-chloro-thiophen-2-yl)-thiazole [prepared by adopting a procedure described by Ewing, William R. et al.; PCT Int. Appl. (2001) 460 pp. WO 0107436 A2] was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole.  
MS (ES<sup>+</sup>): m/e = 532, chloro pattern.

Example 15: 2-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0085]** The title compound was prepared analogously to example 1 with the difference that 2-Bromomethyl-6-chloro-benzo[b]thiophene [prepared by adopting a procedure described by Ewing, William R. et al.; PCT Int. Appl. (1999) 300 pp. WO 9937304 A1; and Ewing, William R. et al. PCT Int. Appl. (2001) 460 pp. WO 0107436 A2] was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole.  
MS (ES<sup>+</sup>): m/e = 499, chloro pattern.

Example 16: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-amide

(i) (3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-carbamic acid tBu ester

**[0086]** A suspension of 5 g (23.3 mmol) Piperidin-4-ylmethyl-carbamic acid tBu ester, 3.85 g (25.7 mmol) 4-Chloro-pyridinehydrochloride in 15 ml n-BuOH/H<sub>2</sub>O/NEt<sub>3</sub> 1:1:1 was boiled under reflux for 3 days. After removal of the solvent under reduced pressure the residue was purified by chromatography on silica with DCM/MeOH 100:1 -> 50:1 -> 10:1 -> 5:1 to yield a white solid.

Yield: 4.3 g.

(ii) C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine

**[0087]** To a solution of 4.58 g (3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-carbamic acid tBu ester in 12 ml DCM, 12 ml of TFA were added at RT. After stirring for 30 min the solution was diluted with 20 ml of toluene and then evaporated under reduced pressure. The residue was codistilled twice with toluene and was used in the subsequent reactions without further purification. The product was obtained as its trifluoroacetate salt.

Yield: 3.3 g.

(iii) -[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3- carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-amide

**[0088]** To a solution of 50 mg 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3- carboxylic acid, 0.3 ml N-NEM in 1 ml DCM, 59 mg TOTU were added and the mixture was stirred for 30 min at RT. Then 36 mg of C-(3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-methylamine trifluoroacetate were added and the reaction was further stirred for 2 h. After the addition of 2 ml sat. NaHCO<sub>3</sub> the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. The residue was purified by preparative HPLC (C18 reverse phase column, elution with a H<sub>2</sub>O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 23 mg MS (ES<sup>+</sup>): m/e = 565, chloro pattern.

Example 17: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-ylmethyl)-amide

(i) (1-Isopropyl-piperidin-4-ylmethyl)-carbamic acid tert-butyl ester

**[0089]** To a solution of 1.0 g Piperidin-4-ylmethyl-carbamic acid tert-butyl ester in 20 ml acetonitrile 2.6 ml acetone and 586 mg Na(CN)BH<sub>3</sub> were added. After stirring for 16 h at RT the solvent was removed under reduced pressure and the residue was partitioned between 30 ml of water and 30 ml of ethylacetate. The organic layer was washed with saturated Na<sub>2</sub>CO<sub>3</sub> solution, water and then was dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent under reduced pressure yielded a white solid.

Yield: 802 mg.

(ii) C-(1-Isopropyl-piperidin-4-yl)-methylamine

**[0090]** To a solution of 802 mg (1-Isopropyl-piperidin-4-ylmethyl)-carbamic acid tert-butyl ester in 5 ml DCM 4 ml of TFA were added at RT. After stirring for 20 h the solution was diluted with 20 ml of toluene and the solvents were evaporated under reduced pressure. The residue was codistilled twice with toluene and used in the subsequent reaction without further purification. The product was obtained as its trifluoroacetate salt.

Yield: 1.7 g

(iii) 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3- carboxylic acid (1-isopropyl-piperidin-4-ylmethyl)-amide

**[0091]** To a solution of 50 mg 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3- carboxylic acid, 0.3 ml N-NEM in 1 ml DCM, 59 mg TOTU were added and the mixture was stirred for 30 min at RT. Then 30 mg C-(1-Isopropyl-piperidin-4-yl)-methylamine trifluoroacetate were added and the reaction was stirred for a further

2 h. After the addition of 2 ml sat.  $\text{NaHCO}_3$  the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a  $\text{H}_2\text{O}/\text{MeCN}$  gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 14 mg MS ( $\text{ES}^+$ ):  $m/e = 530$ , chloro pattern.

Example 18: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-amide

(i) (3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-carbamic acid tert-butyl ester

**[0092]** A solution of 3 g Piperidin-4-yl-carbamic acid tert-butyl ester and 2.5 g 4-Chloropyridine in 9 ml n-butanol/water/ $\text{NEt}_3$  1:1:1 was heated at  $100^\circ\text{C}$  for 48 h. Then the solution was cooled to RT diluted with DCM and washed with  $\text{NaHCO}_3$  solution and water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed under reduced pressure. Chromatographic purification of the residue on silica with DCM as eluent gave after evaporation of the fractions containing the product a white foam.

Yield 1.7g.

(ii) 3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-ylamine

**[0093]** To a solution of 4 g (3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-yl)-carbamic acid tert-butyl ester in 4 ml DCM, 12 ml TFA were added at RT. After stirring for 20 h the solution was diluted with 20 ml of toluene and the solvents were evaporated under reduced pressure. The residue was codistilled twice with toluene and then used in the subsequent reaction without further purification. The product was obtained as its trifluoroacetate salt.

Yield: 2.7 g.

(iii) 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-amide

**[0094]** To a solution of 50 mg 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid, 0.3 ml N-NEM in 1 ml DCM, 59 mg TOTU were added and the mixture was stirred for 30 min at RT. Then 33 mg 3,4,5,6-Tetrahydro-2H-[1,4']bipyridinyl-4-ylamine trifluoroacetate were added and the reaction was further stirred for 2 h. After the addition of 2 ml sat.  $\text{NaHCO}_3$  the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. The residue was purified by preparative HPLC (C18 reverse phase column, elution with a  $\text{H}_2\text{O}/\text{MeCN}$  gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 25 mg MS ( $\text{ES}^+$ ):  $m/e = 551$ , chloro pattern.

Example 19: 2-(4-Chloro-benzyl)-4-cyano-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

**[0095]** The title compound was prepared analogously to example 12 with the difference that 1-Bromomethyl-4-chlorobenzene was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole in the alkylation step. MS ( $\text{ESI}^+$ ):  $m/e = 468$ , chloro pattern.

Example 20: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbonyl)-1H-pyrazole-3-carboxylic acid methyl ester

(i) 1H-Pyrazole-3,5-dicarboxylic acid dimethyl ester

**[0096]** To 12 g of 1H-Pyrazole-3,5-dicarboxylic acid 100 ml HCl in methanol (8M) were added at RT and stirred for 48h. Then the solvents were removed under reduced pressure and the residue codistilled with toluene (2X50 ml). Yield: 14g.

(ii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid dimethyl ester

[0097] To a solution of 1 g 1H-Pyrazole-3,5-dicarboxylic acid diethyl ester ethyl ester in 20 ml of DMF and 188 mg of sodium hydride (60% in oil) were added at RT. After stirring for 20 min at room temperature 1.32 g of 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole were added. The reaction was stirred at room temperature for 3 h. Then 100 ml water were added and the precipitating product was collected by filtration.

Yield: 1.7g.

(iii) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- methyl ester

[0098] To a solution of 1.7 g 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid dimethyl ester in 10 ml water/THF 1:1, 4 ml of a 1M aqueous NaOH were added at RT and the mixture was stirred for 3 h with LCMS reaction control. Then the reaction mixture was acidified to pH 3 with half concentrated HCl and extracted with DCM (3X50 ml). The organic phase was dried over MgSO<sub>4</sub>, filtered and the solvent removed under reduced pressure. The residue was subjected to the next reaction step without further purification.

(iv) 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid methyl ester

[0099] To 1 g 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3- methyl ester in 10 ml DCM and 1.4 ml NEt<sub>3</sub>, 667 mg BOP-Cl were added at RT and the mixture was stirred for 30 min. After addition of 563 mg 1-Isopropyl-piperidin-4-ylamine hydrochloride the mixture was stirred for 16 h. After removal of the solvent under reduced pressure the residue was purified by silica gel chromatography eluting with DCM/MeOH/AcOH/H<sub>2</sub>O 20:10:1:1 to yield a white solid.

Yield: 800 mg MS (ES<sup>+</sup>): m/e = 492, chloro pattern.

Example 21: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid

[0100] To a solution of 800 mg 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid methyl ester in 5 ml water/THF 1:1, 3 ml of a 1M aqueous NaOH were added at RT and the mixture was heated for 10 h at 60 °C. Then the reaction mixture was acidified to pH 3 with half concentrated HCl and extracted with DCM (3X50 ml). The organic phase was dried over MgSO<sub>4</sub>, filtered and the solvent removed under reduced pressure. The residue was purified by preparative HPLC (C18 reverse phase column, elution with a H<sub>2</sub>O/MeCN gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 503 mg MS (ES<sup>+</sup>): m/e = 478, chloro pattern.

Example 22: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carboxylic acid

[0101] This compound was isolated as a by-product in example 21.  
MS (ES<sup>+</sup>): m/e = 478, chloro pattern.

Example 23: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid ethyl ester

[0102] The title compound was prepared analogously to example 20 with the difference that 1H-Pyrazole-3,5-dicarboxylic acid diethyl ester was used instead of 1H-Pyrazole-3,5-dicarboxylic acid diethyl ester.  
MS (ES<sup>+</sup>): m/e = 506, chloro pattern.

Example 24: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carboxylic acid ethyl ester

[0103] This compound was isolated as a by-product in example 23.  
MS (ES<sup>+</sup>): m/e = 506, chloro pattern.

Example 25: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(morpholine-4-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0104] To a solution of 100 mg 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid, 0.5 ml N-NEM in 2 ml DCM, 68 mg TOTU were added and the mixture was stirred for 30 min at RT. Then 49 mg morpholine were added and the reaction was further stirred for 16 h. After the addition of 2 ml sat.  $\text{NaHCO}_3$  the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. The residue was purified by preparative HPLC (C18 reverse phase column, elution with a  $\text{H}_2\text{O}/\text{MeCN}$  gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 73 mg MS ( $\text{ES}^+$ ):  $m/e = 547$ , chloro pattern.

Example 26: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-methylamide

[0105] The title compound was prepared analogously to example 25 with the difference that methyl-amine hydrochloride was used instead of morpholine.

MS ( $\text{ES}^+$ ):  $m/e = 491$ , chloro pattern.

Example 27: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(2-hydroxy-ethyl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide]

[0106] The title compound was prepared analogously to example 25 with the difference that 2-amino-ethanol was used instead of morpholine.

MS ( $\text{ES}^+$ ):  $m/e = 521$ , chloro pattern.

Example 28: [(1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-amino)-acetic acid

[0107] The title compound was prepared analogously to example 25 with the difference that amino-acetic acid hydrochloride was used instead of morpholine.

MS ( $\text{ES}^+$ ):  $m/e = 535$ , chloro pattern.

Example 29: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(5-oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0108] To a solution of 50 mg 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid, 0.1 ml N-NEM in 1 ml DCM, 34 mg TOTU were added and the mixture was stirred for 10 min at RT. Then 10  $\mu\text{l}$  hydrazine hydrate were added and the reaction was further stirred for 2 h. After removal of the solvent under reduced pressure the residue was codistilled with toluene (2X10 ml) and the dissolved in 1 ml THF. Then 91 mg Carbonic acid ditrichloromethyl ester were added at RT and the reaction mixture was stirred for 48 h. After the addition of 2 ml sat.  $\text{NaHCO}_3$  the mixture was filtered through a chem elut® cartridge by elution with ethyl acetate and then concentrated under reduced pressure. The residue was purified by preparative HPLC (C18 reverse phase column, elution with a  $\text{H}_2\text{O}/\text{MeCN}$  gradient with 0.1% TFA). The fractions containing the product were evaporated and lyophilized to yield a white solid. The product was obtained as its trifluoroacetate salt.

Yield: 7 mg MS ( $\text{ES}^+$ ):  $m/e = 518$ , chloro pattern.

Example 30: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0109] The title compound was prepared analogously to example 25 with the difference that 2-piperazin-1-yl-ethanol was used instead of morpholine.

MS ( $\text{ES}^+$ ):  $m/e = 590$ , chloro pattern.



EP 1 433 788 A1

Example 31: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[bis-(2-methoxy-ethyl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide]

[0110] The title compound was prepared analogously to example 25 with the difference that bis-(2-methoxy-ethyl)-amine was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 593, chloro pattern.

Example 32: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid 2-(2-oxo-imidazolidin-1-yl)-ethyl ester

[0111] The title compound was prepared analogously to example 25 with the difference that 1-(2-hydroxy-ethyl)-imidazolidin-2-one was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 590, chloro pattern.

Example 33: [1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-methyl-amino)-acetic acid

[0112] The title compound was prepared analogously to example 25 with the difference that methylamino-acetic acid was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 549, chloro pattern.

Example 34: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(thiomorpholine-4-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0113] The title compound was prepared analogously to example 25 with the difference that thiomorpholine was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 563, chloro pattern.

Example 35: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4-hydroxy-piperidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0114] The title compound was prepared analogously to example 25 with the difference that piperidin-4-ol was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 561, chloro pattern.

Example 36: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0115] The title compound was prepared analogously to example 25 with the difference that pyrrolidin-3-ol was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 547, chloro pattern.

Example 37: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4-hydroxymethyl-piperidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0116] The title compound was prepared analogously to example 25 with the difference that piperidin-4-yl-methanol was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 575, chloro pattern.

Example 38: 5-(8-Aza-spiro[4.5]decane-8-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0117] The title compound was prepared analogously to example 25 with the difference that 8-aza-spiro[4.5]decane hydrochloride was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 599, chloro pattern.

# EP 1 433 788 A1

Example 39: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-methanesulfonyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0118] The title compound was prepared analogously to example 25 with the difference that 3-methanesulfonyl-pyrrolidine was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 609, chloro pattern.

Example 40: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(1,1-dioxo-tetrahydro-1-thiophen-3-yl)-methyl-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide]

[0119] The title compound was prepared analogously to example 25 with the difference that (1,1-Dioxo-tetrahydro-1-thiophen-3-yl)-methyl-amine was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 609, chloro pattern.

Example 41: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-oxo-piperazine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0120] The title compound was prepared analogously to example 25 with the difference that piperazin-2-one was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 560, chloro pattern.

Example 42: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[(1,4)oxazepane-4-carbonyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0121] The title compound was prepared analogously to example 25 with the difference that [1,4]oxazepane was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 561, chloro pattern.

Example 43: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-trifluoromethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0122] The title compound was prepared analogously to example 25 with the difference that 2-trifluoromethyl-pyrrolidine was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 599, chloro pattern.

Example 44: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-[(2-sulfamoyl-ethyl)-amide]

[0123] The title compound was prepared analogously to example 25 with the difference that 2-amino-ethanesulfonic acid amide was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 584, chloro pattern.

Example 45: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-cyclopropylamide 5-[(1-isopropyl-piperidin-4-yl)-amide]

[0124] The title compound was prepared analogously to example 25 with the difference that cyclopropylamine was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 517, chloro pattern.

Example 46: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-cyclobutylamide 5-[(1-isopropyl-piperidin-4-yl)-amide]

[0125] The title compound was prepared analogously to example 25 with the difference that cyclobutylamine was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 531, chloro pattern.

Example 47: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-[(2-methoxy-ethyl)-amide]

[0126] The title compound was prepared analogously to example 25 with the difference that 2-methoxy-ethylamine was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 535, chloro pattern.

Example 48: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0127] The title compound was prepared analogously to example 25 with the difference that pyrrolidine was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 531, chloro pattern.

Example 49: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(cyanamide-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0128] The title compound was prepared analogously to example 25 with the difference that cyanamide was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 502, chloro pattern.

Example 50: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid methyl ester

(I) 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide

[0129] To a solution of 5 g 5-Chloro-pyridin-2-ylamine and 1.5 ml pyridine in 30 ml toluene 8 g bromoacetyl bromide dissolved in 10 ml toluene was added dropwise under ice cooling. After 2 h the precipitate was isolated by filtration and recrystallized from toluene to yield a white solid.

Yield: 12 g.

(II) 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid methyl ester

[0130] The title compound was prepared analogously to example 20 with the difference that 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole in the alkylation step.

MS (ES<sup>+</sup>): m/e = 463, chloro pattern.

Example 51: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid

[0131] The title compound was prepared analogously to example 21 with the difference that 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole in the alkylation step.

MS (ES<sup>+</sup>): m/e = 449, chloro pattern.

Example 52: 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-pyrazole-3,5-dicarboxylic acid 3-cyclobutylamide 5-[(1-isopropyl-piperidin-4-yl)-amide]

[0132] The title compound was prepared analogously to example 46 with the difference that 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide was used instead of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole in the alkylation step.

MS (ES<sup>+</sup>): m/e = 502, chloro pattern.

Example 53: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0133] The title compound was prepared analogously to example 1 with the difference that 3-Trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester was used instead of 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester.

MS (ES<sup>+</sup>): m/e = 502, chloro pattern.

Example 54: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid bis-[(1-isopropyl-piperidin-4-yl)-amide]

[0134] The title compound was prepared analogously to example 25 with the difference that 1-Isopropyl-piperidin-4-ylamine dihydrochloride was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 602, chloro pattern.

Example 55: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0135] The title compound was prepared analogously to example 1 with the difference that 4-Cyano-2H-pyrazole-3-carboxylic acid ethyl ester was used instead of 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester..

MS (ES<sup>+</sup>): m/e = 459, chloro pattern.

Example 56: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0136] This compound was isolated as a by-product in example 55.

MS (ES<sup>+</sup>): m/e = 459, chloro pattern.

Example 57: 2-[(4-Chloro-phenylcarbonyl)-methyl]-4-cyano-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0137] The title compound was prepared analogously to example 1 with the difference that 2-Bromo-N-(4-chloro-phenyl)-acetamide and 4-Cyano-2H-pyrazole-3-carboxylic acid ethyl ester were used instead of 2-Bromo-N-(5-chloro-pyridin-2-yl)-acetamide and 5-Thiophen-2-yl-2H-pyrazole-3-carboxylic acid ethyl ester in the alkylation step.

MS (ESI<sup>+</sup>): m/e = 429, chloro pattern.

Example 58: 3-[(1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbonyl)-1H-pyrazole-3-carbonyl]-amino)-propionic acid

[0138] The title compound was prepared analogously to example 25 with the difference that 3-Amino-propionic acid was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 549, chloro pattern.

Example 59: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-(methoxy-amide)

[0139] The title compound was prepared analogously to example 25 with the difference that O-Methyl-hydroxylamine hydrochloride was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 507, chloro pattern.

Example 60: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-carbamoylmethyl-amide 5-[(1-isopropyl-piperidin-4-yl)-amide]

[0140] The title compound was prepared analogously to example 25 with the difference that 2-Amino-acetamide hydrochloride was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 534, chloro pattern.

Example 61: [(1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbonyl)-1H-pyrazole-3-carbonyl)-amino)-acetic acid ethyl ester

[0141] The title compound was prepared analogously to example 25 with the difference that Amino-acetic acid ethyl ester hydrochloride was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 563, chloro pattern.

Example 62: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(3-hydroxy-propyl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide]

[0142] The title compound was prepared analogously to example 25 with the difference that 3-Amino-propan-1-ol was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 535, chloro pattern.

Example 63: 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-(2S)-azetidine-2-carboxylic acid

[0143] The title compound was prepared analogously to example 25 with the difference that 2S-Azetidine-2-carboxylic acid was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 561, chloro pattern.

Example 64: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2S,2-hydroxymethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0144] The title compound was prepared analogously to example 25 with the difference that 2S-Pyrrolidin-2-yl-methanol was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 561, chloro pattern.

Example 65: 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-2S-pyrrolidine-2-carboxylic acid

[0145] The title compound was prepared analogously to example 25 with the difference that 2S-Pyrrolidine-2-carboxylic acid was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 575, chloro pattern.

Example 66: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2S,2-methoxymethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0146] The title compound was prepared analogously to example 25 with the difference that 2S,2-Methoxymethyl-pyrrolidine was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 575, chloro pattern.

Example 67: 5-(2R,5R,2,5-Bis-methoxymethyl-pyrrolidine-1-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0147] The title compound was prepared analogously to example 25 with the difference that 2R,5R,2,5-Bis-methoxymethyl-pyrrolidine was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 619, chloro pattern.

Example 68: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(4,5-dihydro-oxazol-2-yl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide]

[0148] The title compound was prepared analogously to example 25 with the difference that 4,5-Dihydro-oxazol-2-ylamine hydrochloride was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 546, chloro pattern.

Example 69: 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-piperidine-4-carboxylic acid ethyl ester

[0149] The title compound was prepared analogously to example 25 with the difference that Piperidine-4-carboxylic acid ethyl ester was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 617, chloro pattern.

# EP 1 433 788 A1

Example 70: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-[(2-morpholin-4-yl-ethyl)-amide]

[0150] The title compound was prepared analogously to example 25 with the difference that 2-Morpholin-4-yl-ethyl-amine was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 590, chloro pattern.

Example 71: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4,4-difluoro-piperidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0151] The title compound was prepared analogously to example 25 with the difference that 4,4-Difluoro-piperidine hydrochloride was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 581, chloro pattern.

Example 72: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-oxo-oxazolidine-3-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0152] The title compound was prepared analogously to example 25 with the difference that Oxazolidin-2-one was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 547, chloro pattern.

Example 73: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-[(2-(2-oxo-imidazolidin-1-yl)-ethyl)-amide]

[0153] The title compound was prepared analogously to example 25 with the difference that 1-(2-Amino-ethyl)-imidazolidin-2-one was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 589, chloro pattern.

Example 74: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-[(2,2,2-trifluoro-ethyl)-amide]

[0154] The title compound was prepared analogously to example 25 with the difference that 2,2,2-Trifluoro-ethyl-amine was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 559, chloro pattern.

Example 75: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(1,1-dioxo-tetrahydro-1-thiophen-3-yl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide]

[0155] The title compound was prepared analogously to example 25 with the difference that 1,1-Dioxo-tetrahydro-1-thiophen-3-ylamine was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 595, chloro pattern.

Example 76: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-[(3-(2-oxo-pyrrolidin-1-yl)-propyl)-amide]

[0156] The title compound was prepared analogously to example 25 with the difference that 1-(3-Amino-propyl)-pyrrolidin-2-one was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 602, chloro pattern.

Example 77: 5-(Azetidine-1-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0157] The title compound was prepared analogously to example 25 with the difference that Azetidine was used instead of morpholine.  
MS (ES<sup>+</sup>): m/e = 517, chloro pattern.

## EP 1 433 788 A1

Example 78: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(thiazolidine-3-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0158] The title compound was prepared analogously to example 25 with the difference that Thiazolidine was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 549, chloro pattern.

Example 79: 2-[[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-amino]-3,3,3-trifluoro-propionic acid

[0159] The title compound was prepared analogously to example 25 with the difference that 2-Amino-3,3,3-trifluoro-propionic acid was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 603, chloro pattern.

Example 80: 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-trimethylsilanylmethyl-amide

[0160] The title compound was prepared analogously to example 25 with the difference that C-Trimethylsilanyl-methylamine was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 563, chloro pattern.

Example 81: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[4-(2-oxo-pyrrolidin-1-yl)-piperidine-1-carbonyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0161] The title compound was prepared analogously to example 25 with the difference that 1-Piperidin-4-yl-pyrrolidin-2-one hydrochloride was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 628, chloro pattern.

Example 82: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methanesulfonylaminocarbonyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0162] The title compound was prepared analogously to example 25 with the difference that Methanesulfonamide was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 555, chloro pattern.

Example 83: 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide

[0163] The title compound was prepared analogously to example 25 with the difference that Azetidin-3-ol hydrochloride was used instead of morpholine.

MS (ES<sup>+</sup>): m/e = 533, chloro pattern.

### Pharmacological testing

[0164] The ability of the compounds of the formula I to inhibit factor Xa or factor VIIa or other enzymes like thrombin, plasmin, or trypsin can be assessed by determining the concentration of the compound of the formula I that inhibits enzyme activity by 50 %, i. e. the IC<sub>50</sub> value, which was related to the inhibition constant K<sub>i</sub>. Purified enzymes were used in chromogenic assays. The concentration of inhibitor that causes a 50 % decrease in the rate of substrate hydrolysis was determined by linear regression after plotting the relative rates of hydrolysis (compared to the uninhibited control) versus the log of the concentration of the compound of formula I. For calculating the inhibition constant K<sub>i</sub>, the IC<sub>50</sub> value was corrected for competition with substrate using the formula

$$K_i = IC_{50} / \{1 + (\text{substrate concentration} / K_m)\}$$

wherein K<sub>m</sub> is the Michaelis-Menten constant (Chen and Prusoff, Biochem. Pharmacol. 22 (1973) 3099-3108; I. H. Segal, Enzyme Kinetics, 1975, John Wiley & Sons, New York, 100-125; which were incorporated herein by reference).

## a) Factor Xa Assay

[0165] In the assay for determining the inhibition of factor Xa activity TBS-PEG buffer (50 mM Tris-HCl, pH 7.8, 200 mM NaCl, 0.05 % (w/v) PEG-8000, 0.02 % (w/v) NaN<sub>3</sub>) was used. The IC<sub>50</sub> was determined by combining in appropriate wells of a Costar half-area microtiter plate 25  $\mu$ l human factor Xa (Enzyme Research Laboratories, Inc.; South Bend, Indiana) in TBS-PEG; 40  $\mu$ l 10 % (v/v) DMSO in TBS-PEG (uninhibited control) or various concentrations of the compound to be tested diluted in 10 % (v/v) DMSO in TBS-PEG; and substrate S-2765 (N( $\alpha$ )-benzyloxycarbonyl-D-Arg-Gly-L-Arg-p-nitroanilide; Kabi Pharmacia, Inc.; Franklin, Ohio) in TBS-PEG.

The assay was performed by pre-incubating the compound of formula I plus enzyme for 10 min.

Then the assay was initiated by adding substrate to obtain a final volume of 100  $\mu$ l. The initial velocity of chromogenic substrate hydrolysis was measured by the change in absorbance at 405 nm using a Bio-tek Instruments kinetic plate reader (Ceres UV900HDi) at 25 °C during the linear portion of the time course (usually 1.5 min after addition of substrate). The enzyme concentration was 0.5 nM and substrate concentration was 140  $\mu$ M.

## b) Factor VIIa Assay

[0166] The inhibitory activity towards factor VIIa/tissue factor activity was determined using a chromogenic assay essentially as described previously (J. A. Ostrem et al., Biochemistry 37 (1998) 1053-1059 which was incorporated herein by reference). Kinetic assays were conducted at 25 °C in half-area microtiter plates (Costar Corp., Cambridge, Massachusetts) using a kinetic plate reader (Molecular Devices Spectramax 250). A typical assay consisted of 25  $\mu$ l human factor VIIa and TF (5 nM and 10 nM, respective final concentration) combined with 40  $\mu$ l of inhibitor dilutions in 10% DMSO/TBS-PEG buffer (50 mM Tris, 15 mM NaCl, 5 mM CaCl<sub>2</sub>, 0.05 % PEG 8000, pH 8.15). Following a 15 minute preincubation period, the assay was initiated by the addition of 35  $\mu$ l of the chromogenic substrate S-2288 (D-Ile-Pro-Arg-p-nitroanilide, Pharmacia Hepar Inc., 500  $\mu$ M final concentration). The results (inhibition constants K<sub>i</sub> (FXa) for inhibition of factor Xa) are shown in Table 1.

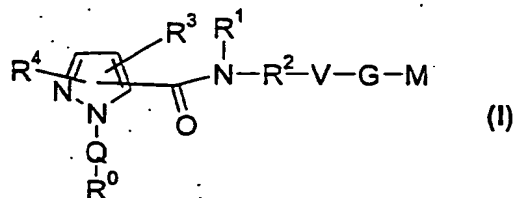
Table1:

Example	K <sub>i</sub> (FXa) [ $\mu$ M]	Example	K <sub>i</sub> (FXa) [ $\mu$ M]	Example	K <sub>i</sub> (FXa) [ $\mu$ M]
1	0,030	20	0,073	40	0,123
2	0,032	21	0,214	41	0,081
3	0,112	23	0,144	42	0,084
5	0,300	25	0,095	43	0,072
6	0,491	26	0,068	44	0,046
7	0,293	27	0,088	45	0,061
8	0,054	28	0,082	46	0,106
9	0,332	29	0,155	47	0,086
10	0,041	30	0,262	48	0,183
11	0,083	31	0,180	49	0,040
12	0,014	32	0,045	50	0,010
13	0,039	33	0,082	52	0,016
14	0,046	34	0,108	55	0,099
15	0,013	35	0,163	56	0,144
16	0,165	36	0,122	57	0,410
17	0,155	37	0,195		
18	0,205	38	0,932		
19	0,274	39	0,145		



## Claims

1. Compound of the formula I,



R<sup>0</sup> is

1) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R<sub>8</sub>,

2) a monocyclic or bicyclic 4- to 15-membered heteroaryl out of the group pyridyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl, benzothiazolyl, benzothiophen, quiazolyl and phenylpyridyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sub>8</sub>, or

3) a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sub>8</sub>, and

which is additionally substituted by a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sub>8</sub>,

R<sub>8</sub> is

1) halogen,

2) -NO<sub>2</sub>,

3) -CN,

4) -C(O)-NH<sub>2</sub>,

5) -OH,

6) -NH<sub>2</sub>,

7) -O-CF<sub>3</sub>

8) a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or -O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl,

9) -(C<sub>1</sub>-C<sub>8</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH<sub>2</sub>, -OH or a methoxy residue, or

10) -O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH<sub>2</sub>, -OH or a methoxy residue,

11) -SO<sub>2</sub>-CH<sub>3</sub> or

12) -SO<sub>2</sub>-CF<sub>3</sub>,

provided that R<sub>8</sub> is at least one halogen, -C(O)-NH<sub>2</sub> or -O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl residue, if R<sup>0</sup> is a monocyclic or bicyclic 6- to 14-membered aryl,

Q

is a direct bond, -(C<sub>0</sub>-C<sub>2</sub>)-alkylene-C(O)-NR<sup>10</sup>-, -NR<sup>10</sup>-C(O)-NR<sup>10</sup>-, -NR<sup>10</sup>-C(O)-, -SO<sub>2</sub>-, -(C<sub>1</sub>-C<sub>8</sub>)-alkylene, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-C(O)NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-C(O)-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-S-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-C(O)-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-SO<sub>2</sub>-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-SO<sub>2</sub>-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-CH(OH)-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-O-C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(C<sub>2</sub>-C<sub>3</sub>)-alkylene-O-(C<sub>0</sub>-C<sub>3</sub>)-alkylene-, -(C<sub>2</sub>-C<sub>3</sub>)-alkylene-S(O)-, -(C<sub>2</sub>-C<sub>3</sub>)-alkylene-S(O)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-C(O)-O-(CH<sub>2</sub>)<sub>n</sub>-, -(C<sub>2</sub>-C<sub>3</sub>)-alkylene-S(O)<sub>2</sub>-NH-(R<sup>10</sup>)-, -(C<sub>2</sub>-C<sub>3</sub>)-alkylene-N(R<sup>10</sup>)- or -(C<sub>0</sub>-C<sub>3</sub>)-alkylene-C(O)-O-,

wherein R<sup>10</sup> is as defined below, and wherein n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6, wherein the alkylene residues which are formed by -(CH<sub>2</sub>)<sub>m</sub>- or -(CH<sub>2</sub>)<sub>n</sub>- are unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH<sub>2</sub> or -OH; or -(C<sub>3</sub>-C<sub>6</sub>)-cycloalkylene, wherein cycloalkylene is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, -NH<sub>2</sub> or -OH; a hydrogen atom, -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sub>13</sub>; -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-C(O)-NH-R<sup>0</sup>, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-C(O)-O-R<sup>15</sup>, a monocyclic or bicyclic

6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R8, wherein R8 is as defined above; a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen; -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkylene, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-S(O)-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-S(O)<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub>)-alkyl, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-S(O)<sub>2</sub>-N(R<sup>4</sup>)-R<sup>5</sup>, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>0</sub>-C<sub>3</sub>)-alkylene-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, or -(C<sub>0</sub>-C<sub>3</sub>)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, whereas R14 is defined below,

R<sup>4</sup> and R<sup>5</sup> are independent of one another are identical or different and are hydrogen atom or -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, R<sup>2</sup> is a direct bond or -(C<sub>1</sub>-C<sub>4</sub>)-alkylene, or

R<sup>1</sup> and R<sup>3</sup> together with the atoms to which they are bonded form a 4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

R<sup>1</sup>-N-R<sup>2</sup>-V form a 4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

R14 is halogen, -OH, =O, -(C<sub>1</sub>-C<sub>8</sub>)-alkyl, -(C<sub>1</sub>-C<sub>4</sub>)-alkoxy, -NO<sub>2</sub>, -C(O)-OH, -CN, -NH<sub>2</sub>, -C(O)-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>1</sub>-C<sub>8</sub>)-alkylsulfonyl, -SO<sub>2</sub>, -C(O)-NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, -C(O)-N-[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, -NR<sup>18</sup>-C(O)-NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, -C(O)-NH<sub>2</sub>, -S-R<sup>18</sup>, or -NR<sup>18</sup>-C(O)-NH-[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, wherein R<sup>18</sup> is hydrogen atom, -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkyl or -(C<sub>1</sub>-C<sub>6</sub>)-alkyl,

V is 1) a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, 2) a 6- to 14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

3) a monocyclic or bicyclic 4- to 15-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

G is a direct bond, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-SO<sub>2</sub>-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-CH(OH)-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-C(O)-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-C(O)-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-S-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-SO<sub>2</sub>-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-, -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-, -(CH<sub>2</sub>)<sub>m</sub>-O-C(O)-NR<sup>10</sup>-(CH<sub>2</sub>)<sub>n</sub>- or -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>-C(O)-O-(CH<sub>2</sub>)<sub>n</sub>-,

n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

R<sup>10</sup> is hydrogen atom, -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkyl or -(C<sub>1</sub>-C<sub>6</sub>)-alkyl,

M is 1) a hydrogen atom, 2) -(C<sub>1</sub>-C<sub>8</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

3) -C(O)-N(R<sup>11</sup>)-R<sup>12</sup>,

4) -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>,

5) -(C<sub>6</sub>-C<sub>14</sub>)-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

6) -(C<sub>4</sub>-C<sub>15</sub>)-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14,

7) -(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, or

8) a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R14, wherein R14 is defined above,

R<sup>11</sup> and R<sup>12</sup> are independently of one another identical or different and are

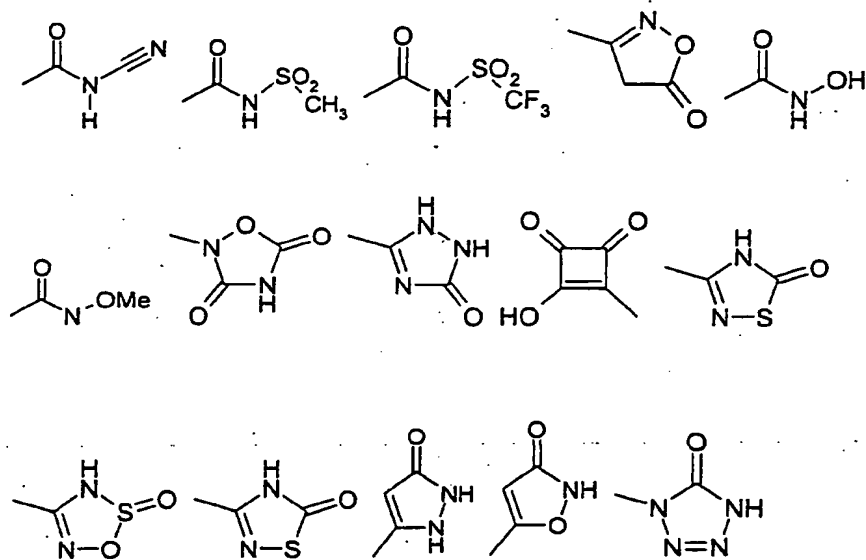
- 1) hydrogen atom,
- 2)  $-(C_1-C_6)$ -alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
- 3)  $-(C_3-C_8)$ -cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
- 4)  $-(C_1-C_4)$ -alkyl- $-(C_6-C_{14})$ -aryl, wherein alkyl and aryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13,
- 5)  $-(C_6-C_{14})$ -aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,
- 6)  $-(C_4-C_{15})$ -heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13 or
- 7)  $-(C_1-C_4)$ -alkyl- $-(C_4-C_{15})$ -heteroaryl, wherein alkyl and heteroaryl independently from one another are unsubstituted or mono-, di- or trisubstituted by R13, or

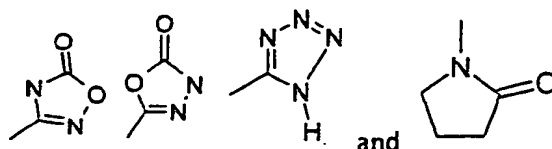
R11 and R12

together with the nitrogen atom to which they are bonded form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

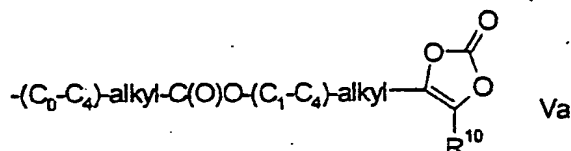
R13 is

halogen,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-(C_0-C_6)$ -alkyl-OH,  $-(C_1-C_8)$ -alkyl,  $-(C_1-C_8)$ -alkoxy,  $-(C_0-C_6)$ -alkyl- $CF_3$ , phenyl, phenyloxy-,  $-(C_0-C_6)$ -alkyl-C(O)-O-R<sup>11</sup>,  $-(C_3-C_8)$ -cycloalkyl, phenyl- $-(C_1-C_4)$ -alkoxy-,  $-(C_0-C_6)$ -alkyl-C(O)-N(R<sup>11</sup>)-R<sup>12</sup>,  $-(C_0-C_6)$ -alkyl-N(R<sup>11</sup>)-R<sup>12</sup>,  $-NR^{10}$ -SO<sub>2</sub>-R<sup>10</sup>,  $-S-R^{10}$ ,  $-S(O)_r-R^{10}$ , wherein r is 1 or 2;  $-(C_0-C_6)$ -alkyl-Si(R<sup>10</sup>)<sub>s</sub>, wherein s is 1, 2 or 3,  $-(C_0-C_6)$ -alkyl-S(O)<sub>r</sub>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl, wherein r is as defined above,  $-(C_0-C_6)$ -alkyl-S(O)<sub>r</sub>-N(R<sup>11</sup>)-R<sup>12</sup>, wherein r is as defined above,  $-C(O)-R^{10}$ ,  $-(C_0-C_4)$ -alkyl-C(O)-O-C(R<sup>15</sup>, R<sup>16</sup>)-O-C(O)-R<sup>17</sup>,  $-CN$ ,  $-(C_0-C_4)$ -alkyl-C(O)-O-C(R<sup>15</sup>, R<sup>16</sup>)-O-C(O)-O-R<sup>17</sup>,  $-(C_1-C_4)$ -perfluoroalkyl,  $-O-R^{15}$ ,  $-O-CF_3$ ,  $-C(O)-O-R^{15}$ ,  $-C(O)-H$ ,  $-NH-C(O)-NH-R^{10}$ ,  $-NH-C(O)-O-R^{15}$ ,  $-(C_1-C_3)$ -alkylene-O-(C<sub>1</sub>-C<sub>3</sub>)-alkyl, or a residue from the following list

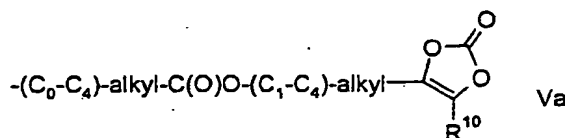




or a residue of formula Va,



- wherein R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are as defined above and R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined below, independently of one another hydrogen,  $-(C_1-C_6)\text{-alkyl}$ , or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by R<sup>10</sup>,
- R<sup>17</sup> is  $-(C_1-C_6)\text{-alkyl}$ ,  $-(C_3-C_8)\text{-cycloalkyl}$ ,  $-(C_1-C_6)\text{-alkyl-(C}_3\text{-C}_8\text{)-cycloalkyl}$  wherein said cycloalkyl ring is unsubstituted or substituted one, two or three times by R<sup>10</sup>, and
- R<sup>3</sup> and R<sup>4</sup> are independent of one another are identical or different and are
- 1) hydrogen atom,
  - 2) halogen,
  - 3)  $-(C_1-C_4)\text{-alkyl}$ , wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,
  - 4)  $-(C_1-C_3)\text{-perfluoroalkyl}$ ,
  - 5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R<sup>13</sup>,
  - 6)  $-O-(C_1-C_4)\text{-alkyl}$ , wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,
  - 7)  $-\text{NO}_2$ ,
  - 8)  $-\text{CN}$ ,
  - 9)  $-\text{OH}$ ,
  - 10) phenyloxy-, wherein phenyloxy is unsubstituted or substituted one to three times by R<sup>13</sup>,
  - 11) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one to three times by R<sup>13</sup>,
  - 12)  $-\text{C(O)-O-R}^{11}$ ,
  - 13)  $-(C_0-C_4)\text{-alkylene-C(O)-N(R}^{11}\text{)-R}^{12}$ ,
  - 14)  $-\text{N(R}^{11}\text{)-R}^{12}$ ,
  - 15)  $-\text{NR}^{10}\text{-SO}_2\text{-R}^{10}$ ,
  - 16)  $-\text{S-R}^{10}$ ,
  - 17)  $-\text{SO}_s\text{-R}^{10}$ , wherein s is 1 or 2,
  - 18)  $-\text{SO}_2\text{-N(R}^{11}\text{)-R}^{12}$ ,
  - 19)  $-\text{C(O)-R}^{10}$ , wherein R<sup>10</sup> is as defined above,
  - 20)  $-\text{C(O)-O-C(R}^{15}, \text{R}^{16}\text{)-O-C(O)-R}^{17}$ , wherein R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined above,
  - 21)  $-\text{C(O)-O-C(R}^{15}, \text{R}^{16}\text{)-O-C(O)-O-R}^{17}$ , wherein R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined above,
  - 22) a residue of formula Va,



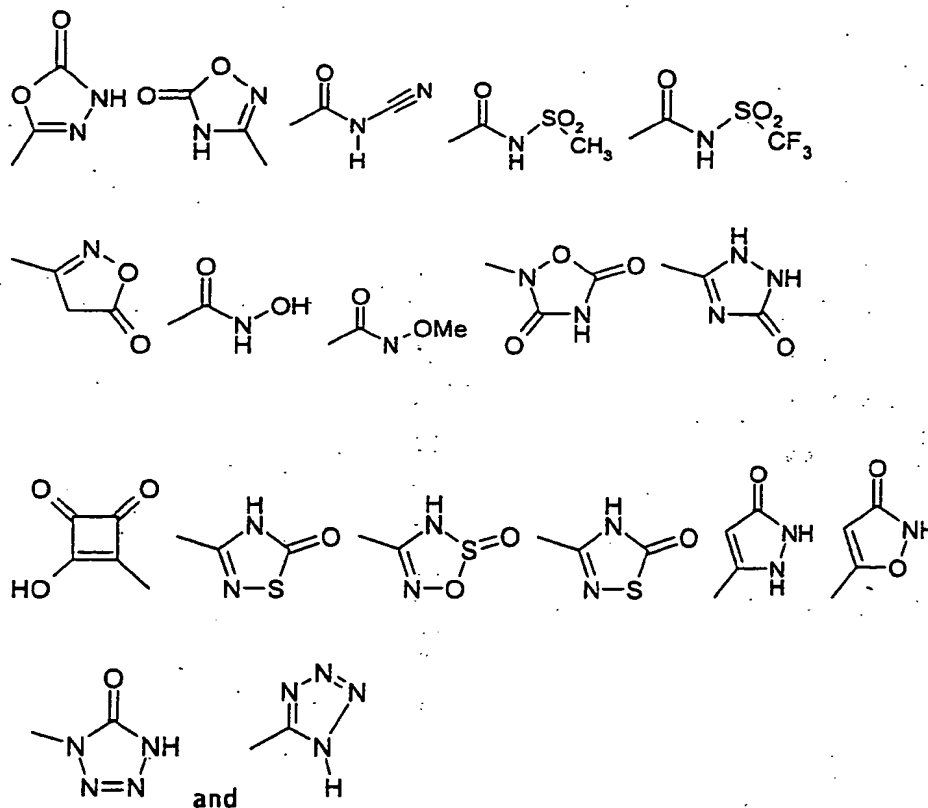
- wherein R<sup>10</sup> is defined as above,
- 23)  $-\text{NR}^{10}\text{-(C}_1\text{-C}_4\text{)-alkyl}$ , wherein alkyl is unsubstituted or substituted one, two or three times by R<sup>13</sup>,

24)

-O-CF<sub>3</sub>,

25)

a residue from the following list



26)

-(C<sub>0</sub>-C<sub>4</sub>)-alkylene-(C<sub>6</sub>-C<sub>14</sub>)-aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by R13 and is as defined above,

27)

-(C<sub>0</sub>-C<sub>4</sub>)-alkylene-(C<sub>4</sub>-C<sub>15</sub>)-heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

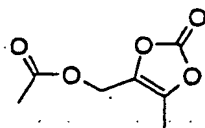
28)

-(C<sub>0</sub>-C<sub>2</sub>)-alkylene-C(O)-O-(C<sub>1</sub>-C<sub>4</sub>)-alkylene-O-C(O)-(C<sub>1</sub>-C<sub>4</sub>)-alkyl,

29)

-(C<sub>0</sub>-C<sub>2</sub>)-alkylene-C(O)-O-(C<sub>1</sub>-C<sub>4</sub>)-alkylene-O-C(O)-O-(C<sub>1</sub>-C<sub>7</sub>)-alkyl,

30)



31)

-(C<sub>0</sub>-C<sub>4</sub>)-alkylene-(C<sub>3</sub>-C<sub>8</sub>)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R13, or

32)

-(C<sub>0</sub>-C<sub>4</sub>)-alkylene-het, wherein het is unsubstituted or mono-, di- or trisubstituted independently of one another by R13,

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

2. Compound of the formula I as claimed in claim 1, wherein

R<sup>0</sup> is 1. a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently

of one another by R<sup>8</sup>,

2. a monocyclic or bicyclic 4- to 14-membered heteroaryl out of the group pyridyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl, benzothiazolyl, benzothiophen, quinazolinyl and phenylpyridyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>, or

3. a monocyclic or bicyclic 4- to 14-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>, and which is additionally substituted by a monocyclic or bicyclic 4- to 14-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>8</sup>,

R<sup>8</sup> is

1. halogen,

2. -NO<sub>2</sub>,

3. -CN,

4. -C(O)-NH<sub>2</sub>,

5. -OH,

6. -NH<sub>2</sub>,

7. -OCF<sub>3</sub>,

8. a monocyclic or bicyclic 4- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by halogen or -O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl,

9. -(C<sub>1</sub>-C<sub>8</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH<sub>2</sub>, -OH or a methoxy residue, or

10. -O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, NH<sub>2</sub>, -OH or a methoxy residue,

11. -SO<sub>2</sub>CH<sub>3</sub> or

12. -SO<sub>2</sub>CF<sub>3</sub>.

provided that R<sup>8</sup> is at least one halogen, -C(O)-NH<sub>2</sub> or -O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl residue, if R<sup>0</sup> is a monocyclic or bicyclic 6- to 14-membered aryl,

Q is a direct bond, -(C<sub>0</sub>-C<sub>2</sub>)-alkylene-C(O)-NR<sup>10</sup>-, -NR<sup>10</sup>-C(O)-NR<sup>10</sup>-, -NR<sup>10</sup>-C(O)-, -SO<sub>2</sub>-, -(C<sub>1</sub>-C<sub>6</sub>)-alkylene,

R<sup>1</sup> is a hydrogen atom, -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>; -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-C(O)-NH-R<sup>0</sup>, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-C(O)-O-R<sup>15</sup>, -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkylene, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-S(O)-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-S(O)<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub>)-alkyl, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-S(O)<sub>2</sub>-N(R<sup>4</sup>)-R<sup>5</sup>, -(C<sub>1</sub>-C<sub>3</sub>)-alkylene-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>0</sub>-C<sub>3</sub>)-alkylene-(C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, or -(C<sub>0</sub>-C<sub>3</sub>)-alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, whereas R<sup>14</sup> is defined below,

R<sup>4</sup> and R<sup>5</sup> are independent of one another are identical or different and are hydrogen atom or -(C<sub>1</sub>-C<sub>4</sub>)-alkyl,

R<sup>2</sup> is a covalent bond or -(C<sub>1</sub>-C<sub>4</sub>)-alkylene, or

R<sup>1</sup> and R<sup>3</sup> together with the atoms to which they are bonded can form a 4- to 7-membered cyclic group, containing up to 1 or 2 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

R<sup>1</sup>-N-R<sup>2</sup>-V can form a 4- to 7-membered cyclic group, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

R<sup>14</sup> is halogen, -OH, =O, -(C<sub>1</sub>-C<sub>8</sub>)-alkyl, -(C<sub>1</sub>-C<sub>4</sub>)-alkoxy, -C(O)-OH, -CN, -NH<sub>2</sub>, -C(O)-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>1</sub>-C<sub>8</sub>)-alkylsulfonyl, -C(O)-NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, -C(O)-N-[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, -NR<sup>10</sup>-C(O)-NH-(C<sub>1</sub>-C<sub>8</sub>)-alkyl, -C(O)-NH<sub>2</sub>-(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkyl, -NR<sup>10</sup>-C(O)-NH-[(C<sub>1</sub>-C<sub>8</sub>)-alkyl]<sub>2</sub>, wherein R<sup>10</sup> is hydrogen atom, or -(C<sub>1</sub>-C<sub>8</sub>)-alkyl,

V is 1. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from

nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ ,

2. a 6- to 14-membered aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ , or

3. a monocyclic or bicyclic 4- to 14-membered heteroaryl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ ,

G is a covalent bond,  $-(CH_2)_m-$ ,  $-(CH_2)_m-O-(CH_2)_n-$ ,  $-(CH_2)_m-C(O)-NR^{10}-(CH_2)_n-$ ,  $-(CH_2)_m-SO_2-(CH_2)_n-$ ,  $-(CH_2)_m-O-C(O)-NR^{10}-(CH_2)_n-$ ,  $-(CH_2)_m-NR^{10}-C(O)-NR^{10}-(CH_2)_n-$ ,  $-(CH_2)_m-C(O)-(CH_2)_n-$ ,  $-(CH_2)_m-SO_2-NR^{10}-(CH_2)_n-$ ,  $-(CH_2)_m-NR^{10}-SO_2-(CH_2)_n-$ ,  $-(CH_2)_m-NR^{10}$ , or  $-(CH_2)_m-NR^{10}-C(O)-O-(CH_2)_n-$ , n and m are independently of one another identical or different and are the integers zero, 1, 2, 3, 4, 5 or 6,

$R^{10}$  is hydrogen atom,  $-(C_1-C_3)$ -perfluoroalkyl or  $-(C_1-C_6)$ -alkyl,

M is 1. a hydrogen atom,  
2.  $-(C_1-C_6)$ -alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ ,  
3.  $-C(O)-NR^{11}R^{12}$ ,  
4.  $-(CH_2)_m-NR^{10}$ ,  
5.  $-(C_6-C_{14})$ -aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ ,  
6.  $-(C_4-C_{14})$ -heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ ,  
7.  $(C_3-C_7)$ -cycloalkyl, wherein said cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ , or

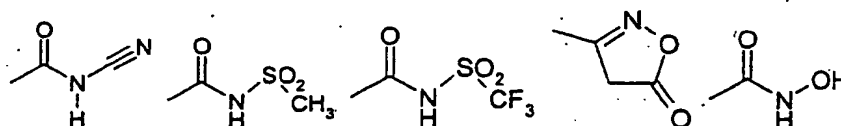
8. a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ , wherein  $R^{14}$  is defined above,

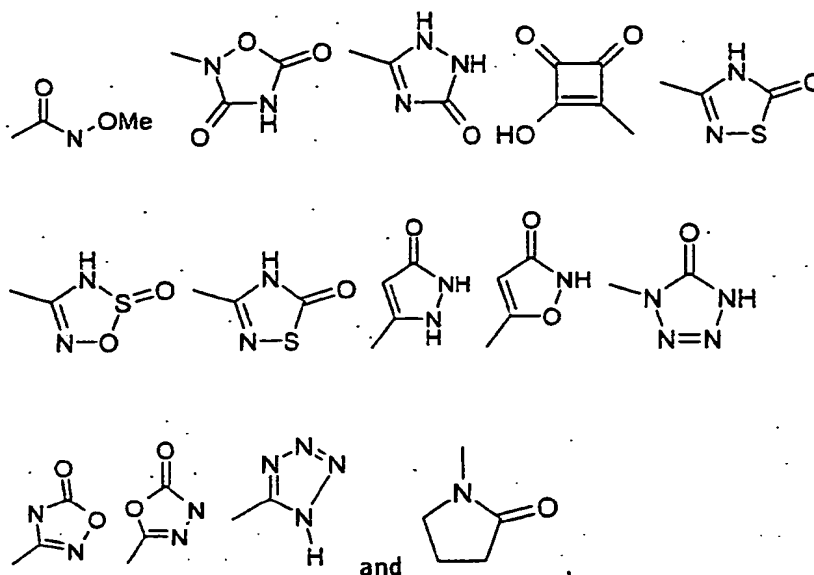
$R^{11}$  and  $R^{12}$  are independently of one another identical or different and are

1) hydrogen atom,  
2)  $-(C_1-C_6)$ -alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ,  
3)  $-(C_3-C_6)$ -cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ,  
4)  $-(C_0-C_4)$ -alkyl- $-(C_4-C_{15})$ -heteroaryl, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ , or

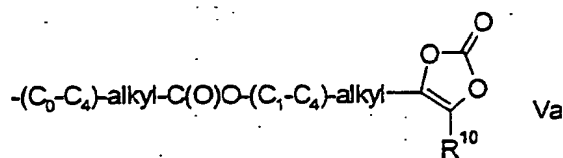
$R^{11}$  and  $R^{12}$  together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen; wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ,

$R^{13}$  is halogen,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-(C_0-C_6)$ -alkyl-OH,  $-(C_1-C_6)$ -alkyl,  $-(C_1-C_6)$ -alkoxy,  $-(C_0-C_6)$ -alkyl- $CF_3$ , phenyl, phenyloxy-,  $-(C_0-C_6)$ -alkyl-C(O)-O- $R^{11}$ ,  $-(C_3-C_6)$ -cycloalkyl, phenyl- $-(C_1-C_4)$ -alkoxy-,  $-(C_0-C_6)$ -alkyl-C(O)-N( $R^{11}$ )- $R^{12}$ ,  $-(C_0-C_6)$ -alkyl-N( $R^{11}$ )- $R^{12}$ ,  $-NR^{10}-SO_2-R^{10}$ ,  $-S-R^{10}$ ,  $-S(O)_r-R^{10}$ , wherein r is 1 or 2;  $-(C_0-C_6)$ -alkyl-Si( $R^{10}$ )<sub>s</sub>, wherein s is 1, 2 or 3,  $-(C_0-C_6)$ -alkyl-S(O)<sub>r</sub>- $-(C_0-C_6)$ -alkyl, wherein r is as defined above,  $-(C_0-C_6)$ -alkyl-S(O)<sub>r</sub>-N( $R^{11}$ )- $R^{12}$ , wherein r is as defined above,  $-C(O)-R^{10}$ ,  $-(C_0-C_4)$ -alkyl-C(O)-O-C( $R^{15}$ ,  $R^{16}$ )-O-C(O)- $R^{17}$ ,  $-CN$ ,  $-(C_0-C_4)$ -alkyl-C(O)-O-C( $R^{15}$ ,  $R^{16}$ )-O-C(O)-O- $R^{17}$ ,  $-(C_1-C_4)$ -perfluoroalkyl,  $-O-R^{15}$ ,  $-O-CF_3$ ,  $-C(O)-O-R^{15}$ ,  $-C(O)-H$ ,  $-NH-C(O)-NH-R^{10}$ ,  $-NH-C(O)-O-R^{15}$ ,  $-(C_1-C_3)$ -alkylene-O- $-(C_1-C_3)$ -alkyl, or a residue from the following list





or a residue of formula Va,



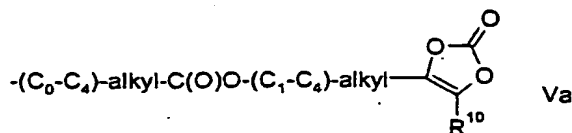
wherein  $\text{R}^{10}$ ,  $\text{R}^{11}$ ,  $\text{R}^{12}$  are as defined above and  $\text{R}^{15}$ ,  $\text{R}^{16}$  or  $\text{R}^{17}$  are as defined below, independently of one another hydrogen,  $-(\text{C}_1-\text{C}_6)\text{-alkyl}$ , or together with the carbon atom to which they are bonded they can form a 3- to 6 membered carbocyclic ring which is unsubstituted or substituted one to three times by  $\text{R}^{10}$ ,  
 $\text{R}^{17}$  is  $-(\text{C}_1-\text{C}_6)\text{-alkyl}$ ,  $-(\text{C}_1-\text{C}_8)\text{-cycloalkyl}$ ,  $-(\text{C}_1-\text{C}_6)\text{-alkyl}-(\text{C}_1-\text{C}_8)\text{-cycloalkyl}$  wherein said cycloalkyl ring is unsubstituted or substituted one to three times by  $\text{R}^{10}$ , and  
 $\text{R}^3$  and  $\text{R}^4$  are independent of one another are identical or different and are

- 1) hydrogen atom,
- 2) halogen,
- 3)  $-(\text{C}_1-\text{C}_4)\text{-alkyl}$ , wherein alkyl is unsubstituted or substituted one to three times by  $\text{R}^{13}$ ,
- 4)  $-(\text{C}_1-\text{C}_3)\text{-perfluoroalkyl}$ ,
- 5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by  $\text{R}^{13}$ ,
- 6)  $-\text{O}-(\text{C}_1-\text{C}_4)\text{-alkyl}$ , wherein alkyl is unsubstituted or substituted one to three times by  $\text{R}^{13}$ ,
- 7)  $-\text{CN}$ ,
- 8)  $-\text{OH}$ ,
- 9) phenyloxy-, wherein phenyloxy is unsubstituted or substituted one to three times by  $\text{R}^{13}$ ,
- 10) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one to three times by  $\text{R}^{13}$ ,
- 11)  $-\text{C}(\text{O})-\text{O}-\text{R}^{11}$ ,
- 12)  $-(\text{C}_0-\text{C}_4)\text{alkyl}-\text{C}(\text{O})-\text{N}-\text{R}^{11}\text{R}^{12}$ ,
- 13)  $-\text{NR}^{11}\text{R}^{12}$ ,
- 14)  $-\text{NR}^{10}-\text{SO}_2-\text{R}^{10}$ ,
- 15)  $-\text{SO}_n-\text{R}^{10}$ , wherein n is 1 or 2,
- 16)  $-\text{SO}_2-\text{NR}^{11}\text{R}^{12}$ ,



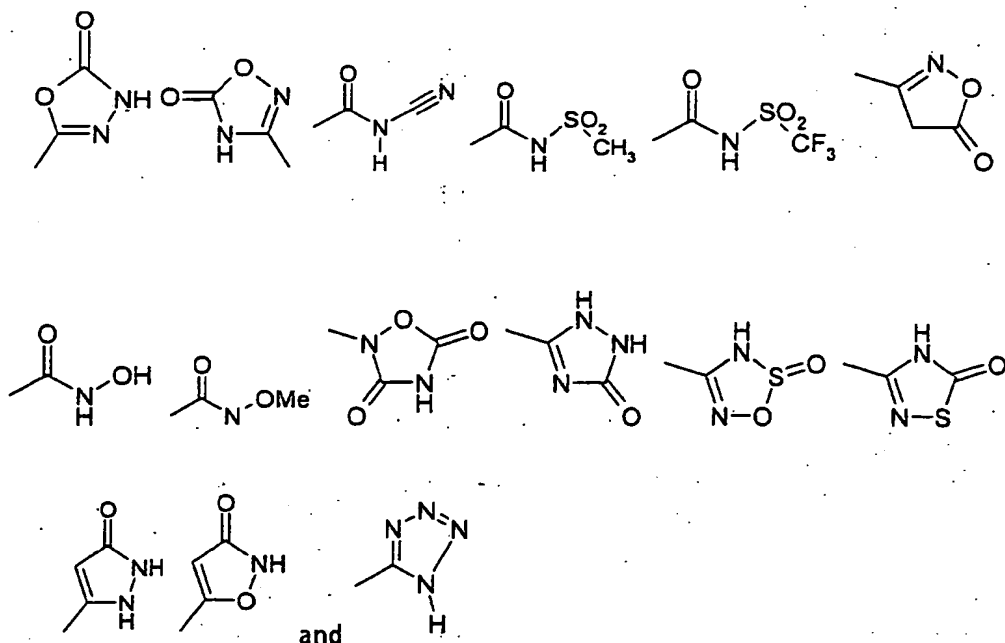
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- 17)  $-C(O)-O-C(R^{15}R^{16})-O-C(O)-R^{17}$ , wherein  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are as defined above,  
 18)  $-C(O)-O-C(R^{15}R^{16})-O-C(O)O-R^{17}$ , wherein  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are as defined above,  
 19) residue of formula Va,

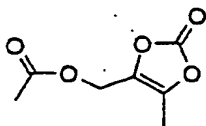


wherein  $R^{10}$  is defined as above,

- 20)  $-NR^{10}-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or substituted one to three times by  $R^{13}$ ,  
 21)  $-OCF_3$ ,  
 22) a residue from the following list



- 23)  $-(C_0-C_2)$ -alkylene-aryl, wherein aryl is a monocyclic or bicyclic 6- to 14-membered aryl, wherein aryl is mono-, di- or trisubstituted independently of one another by  $R^{13}$ , wherein  $R^{13}$  is as defined above,  
 24)  $-(C_0-C_2)$ -alkylene-heteroaryl, wherein heteroaryl is a monocyclic or bicyclic 4- to 15-membered heteroaryl, containing one, two, three or four heteroatoms chosen from nitrogen, sulfur or oxygen,  
 wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ,  
 25)  $-(C_0-C_2)$ alkyl- $C(O)-O-(C_1-C_4)$ -alkyl- $O-C(O)-(C_1-C_4)$ -alkyl,  
 26)  $-(C_0-C_2)$ alkyl- $C(O)-O-(C_1-C_4)$ -alkyl- $O-C(O)O-(C_1-C_7)$ -alkyl,  
 27)



28)  $-(C_0-C_2)$ -alkylene- $(C_3-C_8)$ -cycloalkyl,  $-(C_0-C_3)$ -alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ,

29)  $-(C_0-C_2)$ -alkylene-het, wherein het is a 3- to 7-membered cyclic residue, containing up to 1, 2, 3 or 4 heteroatoms chosen from nitrogen, sulfur or oxygen, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ,

wherein  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are as defined above, in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

### 3. Compound of the formula I as claimed in claims 1 or 2, wherein

$R^0$  is 1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^8$ ,

2. a bicyclic 5- to 14-membered heteroaryl selected out of the group benzimidazolyl, 1,3-benzodioxolyl, benzofuranyl, benzothienophenyl, benzothiazolyl, benzoxazolyl, chromanyl, cinnolyl, indazolyl, indolyl, isochromanyl, isoindolyl, isoquinolyl, phthalazinyl, pteridinyl, purinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, pyridyl, quinazolyl, quinolyl and quinoxalyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^8$ , and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyridazinyl, thiophenyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^8$

3. a monocyclic 5- to 14-membered heteroaryl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^8$ , and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl, thiophenyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^8$

$R^8$  is 1. F, Cl, Br or J,

2.  $-C(O)-NH_2$ ,

3.  $-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen,  $-OH$  or a methoxy residue, or

4.  $-O-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or a methoxy residue,

provided that  $R^8$  is at least one halogen,  $-C(O)-NH_2$  or  $-O-(C_1-C_8)$ -alkyl residue, if  $R^0$  is phenyl,

Q is a direct bond,  $-C(O)-$ ,  $-SO_2-$  or  $-(C_1-C_6)$ -alkylene;  $-(C_0-C_2)$ -alkylene- $C(O)-NR^{10}$ ,

$R^1$  is hydrogen atom or  $-(C_1-C_2)$ -alkyl,  $-(C_1-C_3)$ -alkylene- $C(O)-NH-R^0$ ,  $-(C_1-C_3)$ -alkylene- $C(O)-O-R^{15}$ ,  $-(C_1-C_3)$ -perfluoroalkylene,  $-(C_1-C_3)$ -alkylene- $S(O)_2-(C_1-C_3)$ -alkyl or  $-(C_1-C_3)$ -alkylene- $S(O)_2-N(R^4)-R^5$ ,

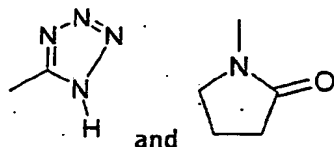
$R^2$  is a direct bond or  $-(C_1-C_2)$ -alkylene, or

$R^1-N-R^2-V$  can form a 4- to 7-membered cyclic group out of the group azetidine, azetidinone, piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine,

- 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,
- 5 R<sup>14</sup> is halogen, -OH, =O, -(C<sub>1</sub>-C<sub>6</sub>)-alkyl, -C(O)-OH, -CN, -NH<sub>2</sub>, -C(O)-O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>1</sub>-C<sub>6</sub>)-alkyl-sulfonyl, -C(O)-NH-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, -C(O)-N-[(C<sub>1</sub>-C<sub>6</sub>)-alkyl]<sub>2</sub>, -C(O)-NH<sub>2</sub>, -NR<sup>10</sup> wherein R<sup>10</sup> is hydrogen atom, -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkyl or -(C<sub>1</sub>-C<sub>6</sub>)-alkyl,
- V is
- 10 1. a 3- to 7-membered cyclic residue out of the group containing compounds which are derived from aziridine, azirine, azetidine, azetidinone, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, tetrazine, tetrazole, azepine, diazirine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,
- 15 2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, or
- 20 3. a bicyclic 5- to 14-membered heteroaryl out of the group quinolyl, isoquinolyl and quinoxaliny, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,
- G is
- 25 a direct bond, -(CH<sub>2</sub>)<sub>m</sub>, or -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>10</sup>,
- m is the integers zero, 1, 2, 3 or 4,
- R<sup>10</sup> is hydrogen atom, -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkyl or -(C<sub>1</sub>-C<sub>4</sub>)-alkyl,
- M is
- 30 1. a hydrogen atom,
2. -(C<sub>6</sub>-C<sub>14</sub>)-heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, thiadiazole or thiomorpholine, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,
- 35 3. -(C<sub>1</sub>-C<sub>6</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, or
4. (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl,
- 40 R<sup>11</sup> and R<sup>12</sup> are independently of one another identical or different and are
- 1) hydrogen atom,
- 2) -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,
- 45 3) -(C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,
- 4) -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-(C<sub>4</sub>-C<sub>15</sub>)-heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from azaspirodecane, azetidine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, dihydrooxazol, imidazole, imidazolidine, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazepane, oxazole, oxazolidine, piperazine, piperidine, pyrazine, pyrazole, pyridazine, pyridine, pyridonyl, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, tetrazine, tetrazole, thiadiazole, thiazole, thiazolidine, thiomorpholine, thiophenyl, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,
- 50 together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring, wherein said heterocyclic ring is a residue out of the group which can be derived from azaspirodecane, azetidine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, dihydrooxazol, imidazole, imidazolidine, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazepane, oxazole, oxazolidine, piperazine, piperidine,
- 55 R<sup>11</sup> and R<sup>12</sup>

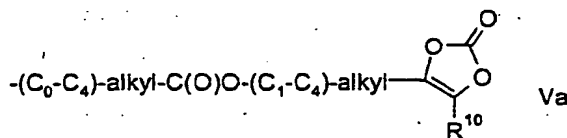
pyrazine, pyrazole, pyridazine, pyridine, pyridonyl, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, tetrazine, tetrazole, thiadiazole, thiazole, thiazolidine, thiomorpholine, thiophenyl, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>13</sup>,

R<sup>13</sup> is Cl, -CN, =O, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-OH, -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, -(C<sub>1</sub>-C<sub>4</sub>)-alkoxy, -(C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-CF<sub>3</sub>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-C(O)-O-R<sup>11</sup>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-C(O)-N(R<sup>11</sup>)-R<sup>12</sup>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-N(R<sup>11</sup>)-R<sup>12</sup>, -S(O)<sub>2</sub>-CH<sub>3</sub>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-Si-(CH<sub>3</sub>)<sub>3</sub>, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-S(O)<sub>r</sub>-(C<sub>0</sub>-C<sub>4</sub>)-alkyl, wherein r is 2, -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-S(O)<sub>r</sub>-N(R<sup>11</sup>)-R<sup>12</sup>, wherein r is 2, -(C<sub>1</sub>-C<sub>2</sub>)-alkylene-O-(C<sub>1</sub>-C<sub>2</sub>)-alkyl or a residue from the following list



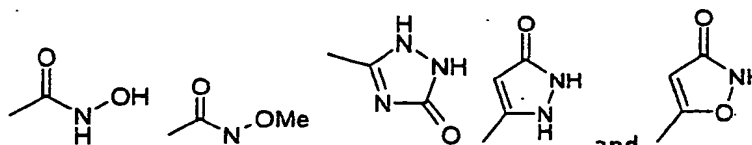
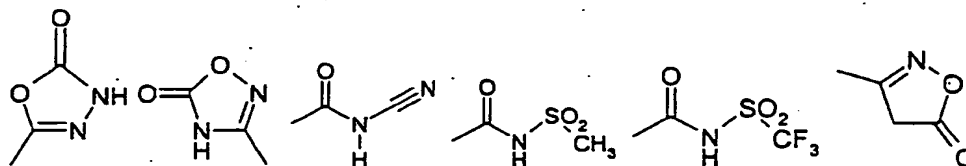
R<sup>15</sup>, R<sup>16</sup> or R<sup>17</sup> are independently of one another hydrogen or -(C<sub>1</sub>-C<sub>6</sub>)-alkyl, R<sup>3</sup> and R<sup>4</sup>, are independent of one another are identical or different and are

- 1) hydrogen atom,
- 2) halogen,
- 3) -(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,
- 4) -(C<sub>1</sub>-C<sub>3</sub>)-perfluoroalkyl,
- 5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R<sup>13</sup>,
- 6) -O-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,
- 7) -CN,
- 8) -OH,
- 9) phenyloxy-, wherein phenyloxy is unsubstituted or substituted one to three times by R<sup>13</sup>,
- 10) benzyloxy-, wherein benzyloxy is unsubstituted or substituted one to three times by R<sup>13</sup>,
- 11) -C(O)-O-R<sup>11</sup>,
- 12) -(C<sub>0</sub>-C<sub>4</sub>)-alkyl-C(O)-N-R<sup>11</sup>R<sup>12</sup>,
- 13) -NR<sup>11</sup>R<sup>12</sup>,
- 14) -NR<sup>10</sup>-SO<sub>2</sub>-R<sup>10</sup>,
- 15) -SO<sub>n</sub>-R<sup>10</sup>, wherein n is 1 or 2,
- 16) -SO<sub>2</sub>-NR<sup>11</sup>R<sup>12</sup>,
- 17) -C(O)-O-C(R<sup>15</sup>R<sup>16</sup>)-O-C(O)-R<sup>17</sup>, wherein R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined above,
- 18) -C(O)-O-C(R<sup>15</sup>R<sup>16</sup>)-O-C(O)-O-R<sup>17</sup>, wherein R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined above,
- 19) residue of formula Va,

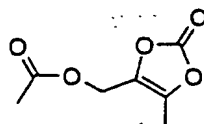


wherein R<sup>10</sup> is defined as above,

- 20) -NR<sup>10</sup>-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,
- 21) -OCF<sub>3</sub>, or
- 22) a residue from the following list



- 23)  $-(C_0-C_2)\text{alkyl}-C(O)-O-(C_1-C_4)\text{-alkyl}-O-C(O)-(C_1-C_4)\text{-alkyl}$ ,  
 24)  $-(C_0-C_2)\text{-alkylene}-C(O)-O-(C_1-C_4)\text{-alkylene}-O-C(O)-O-(C_1-C_7)\text{-alkyl}$  or  
 25)



wherein  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{15}$ ,  $R^{16}$  or  $R^{17}$  are as defined above,  
 in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

4. Compounds of the formula I as claimed in one or more of claims 1 to 3, wherein

- $R^0$  is
1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^8$ ,
  2. a bicyclic 5- to 14-membered heteroaryl selected out of the group indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinoliny, isoquinoliny, chromanyl, isochromanyl, cinnoliny, guinazoliny, quinoxaliny, phthalaziny, pyridoimidazolyl, pyridopyridiny, pyridopyrimidiny, puriny and pteridiny, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^8$ ,  
 and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, thiophenyl, pyrimidinyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^8$ ,
  3. a monocyclic 5- to 14-membered heteroaryl out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^8$ ,  
 and in addition is substituted by a residue selected out of the group pyridyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, 2-furyl, 3-furyl; thienyl, 2-thienyl, 3-thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiophenyl, thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridazinyl and pyrazinyl, wherein said residue is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^8$
- $R^8$  is
1. halogen, such as F, Cl, Br or I,
  2.  $-C(O)-NH_2$ ,
  3.  $-(C_1-C_4)\text{-alkyl}$ , wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen,  $-OH$  or a methoxy residue, or
  4.  $-O-(C_1-C_4)\text{-alkyl}$ , wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another

by halogen or a methoxy residue,

provided that  $R^8$  is at least one halogen,  $-C(O)-NH_2$  or  $-O-(C_1-C_6)$ -alkyl residue, if  $R^0$  is a phenyl,

Q is a direct bond,  $-C(O)-$ ,  $-SO_2-$  or  $-(C_1-C_6)$ -alkylen-,  $-(C_0-C_2)$ -alkylen- $C(O)-NR^{10}$ ,

$R^1$  is hydrogen atom or  $-(C_1-C_2)$ -alkyl,

$R^2$  is a direct bond or  $-(C_1-C_2)$ -alkylen-, or

$R^1-N-R^2-V$  can form a 5- to 7- membered cyclic group out of the group piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, thiadiazole or thiomorpholine, wherein said cyclic group is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{14}$ ,

$R^{14}$  is halogen,  $-(C_1-C_4)$ -alkyl or  $-NH_2$ ,

$R^{11}$  and  $R^{12}$  are independently of one another identical or different and are

1) hydrogen atom,

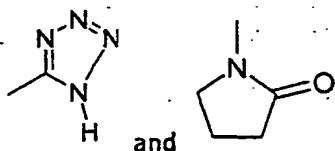
2)  $-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ,

3)  $-(C_3-C_6)$ -cycloalkyl, wherein cycloalkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ,

4)  $-(C_0-C_4)$ -alkyl- $-(C_4-C_{15})$ -heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from azaspirodecane, azetidine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, dihydrooxazol, imidazole, imidazolidine, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazepane, oxazole, oxazolidine, piperazine, piperidine, pyrazine, pyrazole, pyridazine, pyridine, pyridonyl, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, tetrazine, tetrazole, thiadiazole, thiazole, thiazolidine, thiomorpholine, thiophenyl, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ;

$R^{11}$  and  $R^{12}$  together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring, wherein said heterocyclic ring is a residue out of the group which can be derived from azaspirodecane, azetidine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, dihydrooxazol, imidazole, imidazolidine, isothiazole, isoxazole, isoxazolidine, 2-isoxazoline, ketopiperazine, morpholine, oxazepane, oxazole, oxazolidine, piperazine, piperidine, pyrazine, pyrazole, pyridazine, pyridine, pyridonyl, pyrimidine, pyrrolidine, pyrrolidinone, tetrahydropyran, tetrazine, tetrazole, thiadiazole, thiazole, thiazolidine, thiomorpholine, thiophenyl, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole or 1,2,4-triazole, wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ,

$-R^{13}$  is Cl,  $-CN$ ,  $=O$ ,  $-(C_0-C_4)$ -alkyl-OH,  $-(C_1-C_4)$ -alkyl,  $-(C_1-C_4)$ -alkoxy,  $-(C_3-C_6)$ -cycloalkyl,  $-(C_0-C_4)$ -alkyl- $CF_3$ ,  $-(C_0-C_4)$ -alkyl- $C(O)-O-R^{11}$ ,  $-(C_0-C_4)$ -alkyl- $C(O)-N(R^{11})-R^{12}$ ,  $-(C_0-C_4)$ -alkyl- $N(R^{11})-R^{12}$ ,  $S(O)_2-CH_3$ ,  $-(C_0-C_4)$ -alkyl-Si- $(CH_3)_3$ ,  $-(C_0-C_4)$ -alkyl-S(O)- $-(C_0-C_4)$ -alkyl, wherein r is 2,  $-(C_0-C_4)$ -alkyl-S(O)- $N(R^{11})-R^{12}$ , wherein r is 2,  $-(C_1-C_2)$ -alkylene-O- $-(C_1-C_2)$ -alkyl or a residue from the following list



V is

1. a 3- to 7-membered cyclic residue out of the group containing compounds, which are derived from aziridine, azirine, azetidine, pyrrole, pyrrolidine, pyridonyl, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine,

tetrazine, tetrazole, azepine, diazine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, pyridazine, piperidine, piperazine, pyrrolidinone, ketopiperazine, furan, pyran, dioxole, oxazole, isoxazole, 2-isoxazoline, isoxazolidine, morpholine, oxirane, oxaziridine, 1,3-dioxolene, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, oxaziridine, thiophene, thiopyran, thietan, thiazole, isothiazole, isothiazoline, isothiazolidine, 1,2-oxathiolan, thiopyran, 1,2-thiazine, 1,3-thiazole, 1,3-thiazine, 1,4-thiazine, thiadiazine or thiomorpholine, wherein said cyclic residue is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, or

3. a bicyclic 5- to 14-membered heteroaryl out of the group quinolyl, isoquinolyl and quinoxaliny, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

G is a direct bond,  $-(CH_2)_m-$ , or  $-(CH_2)_m-NR^{10}-$ ,

m is the integers zero, 1, 2, 3 or 4,

R<sup>10</sup> is hydrogen atom,  $-(C_1-C_3)$ -perfluoroalkyl or  $-(C_1-C_4)$ -alkyl,

M is 1. a hydrogen atom,

2.  $-(C_6-C_{14})$ -heteroaryl, wherein heteroaryl is a residue out of the group which can be derived from piperidine, piperazine, pyridine, pyrimidine, pyrrolidine, pyrrolidinone, pyridonyl, imidazole, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazole, 1,2,4-triazole, tetrazine, tetrazole, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azepine, ketopiperazine, oxazole, isoxazole, isoxazolidine, 2-isoxazoline, morpholine, thiazole, isothiazole, tetrahydropyran, thiadiazole or thiomorpholine, wherein said heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>,

3.  $-(C_1-C_6)$ -alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R<sup>14</sup>, or

4.  $(C_3-C_6)$ -cycloalkyl,

R<sup>3</sup> and R<sup>4</sup> are independent of one another are identical or different and are

1) hydrogen atom,

2) halogen,

3)  $-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,

4)  $-(C_1-C_3)$ -perfluoroalkyl,

5) phenyl, wherein phenyl is unsubstituted or substituted one to three times by R<sup>13</sup>,

6)  $-O-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,

7) -CN,

8) -OH,

9)  $-C(O)-O-R^{11}$ ,

10)  $-(C_0-C_4)$ alkyl-C(O)-N-R<sup>11</sup>R<sup>12</sup>,

11) -NR<sup>11</sup>R<sup>12</sup>,

12) -NR<sup>10</sup>-SO<sub>2</sub>-R<sup>10</sup>,

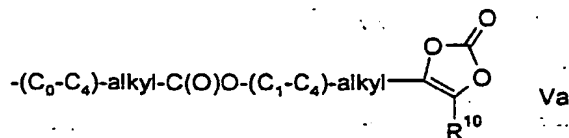
13) -SO<sub>n</sub>-R<sup>10</sup>, wherein n is 1 or 2,

14) -SO<sub>2</sub>-NR<sup>11</sup>R<sup>12</sup>,

15)  $-C(O)-O-C(R^{15}R^{16})-O-C(O)-R^{17}$ , wherein R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined above,

16)  $-C(O)-O-C(R^{15}R^{16})-O-C(O)-R^{17}$ , wherein R<sup>15</sup>, R<sup>16</sup> and R<sup>17</sup> are as defined above,

17) residue of formula Va,

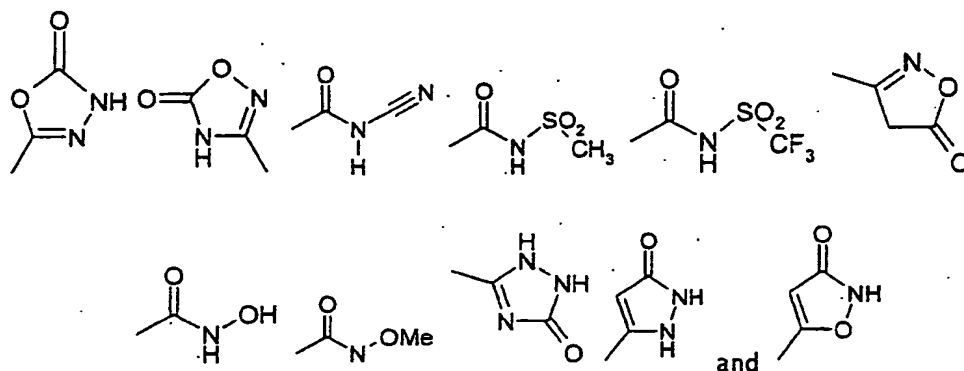


wherein R<sup>10</sup> is defined as above,

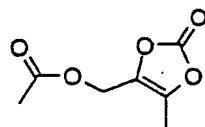
18) -NR<sup>10</sup>-(C<sub>1</sub>-C<sub>4</sub>)-alkyl, wherein alkyl is unsubstituted or substituted one to three times by R<sup>13</sup>,

19)  $-\text{OCF}_3$ , or

20) a residue from the following list

21)  $-(\text{C}_0\text{-C}_2)\text{alkyl-C(O)-O-(C}_1\text{-C}_4\text{)-alkyl-O-C(O)-(C}_1\text{-C}_4\text{)-alkyl}$ ,22)  $-(\text{C}_0\text{-C}_2)\text{alkyl-C(O)-O-(C}_1\text{-C}_4\text{)-alkyl-O-C(O)O-(C}_1\text{-C}_7\text{)-alkyl}$ , or

23)



wherein  $\text{R}^{10}$ ,  $\text{R}^{11}$ ,  $\text{R}^{12}$ ,  $\text{R}^{15}$ ,  $\text{R}^{16}$  or  $\text{R}^{17}$  are as defined above, in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

5. Compound of the formula I as claimed in one or more of claims 1 to 4, wherein

$\text{R}^0$  is

1. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by  $\text{R}^8$ , or
2. a monocyclic 4- to 14-membered heteroaryl out of the group thienyl, thiadiazolyl, isoxazolyl and thiazolyl, wherein said heteroaryl is substituted by a residue selected out of the group thiophenyl, thienyl, 2-thienyl and 3-thienyl, wherein said residue is unsubstituted or mono- or disubstituted independently of one another by  $\text{R}^8$ ,

$\text{R}^8$  is F, Cl, Br,  $-\text{OCH}_3$ ,  $-\text{C(O)-NH}_2$  or  $-\text{O-CF}_3$ ,

Q is a direct bond,  $-\text{C(O)-}$ ,  $-\text{SO}_2-$ , methylene or ethylene,

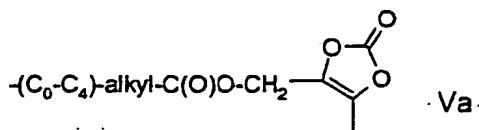
$\text{R}^1$  is hydrogen atom,

$\text{R}^2$  is a direct bond or methylene, or

$\text{R}^1\text{-N-R}^2\text{-V}$  can form a 4- to 7-membered cyclic group out of the group azetidine, pyrrolidine, piperidine and piperazine,

$\text{R}^{13}$  is  $-\text{OH}$ ,  $=\text{O}$ ,  $-\text{F}$ ,  $-\text{CF}_3$ ,  $-\text{C(O)-O-R}^{11}$ ,  $-\text{C(O)-N-R}^{11}\text{R}^{12}$ ,  $-\text{NR}^{11}\text{R}^{12}$ ,  $-\text{NR}^{10}\text{-SO}_2\text{-R}^{10}$ ,  $-\text{SO}_n\text{-R}^{10}$ , wherein n is 1, 2 or 3;  $-(\text{C}_1\text{-C}_6)\text{-alkyl}$ ,  $-(\text{C}_0\text{-C}_3)\text{-alkyl-O-(C}_0\text{-C}_4\text{)-alkyl}$ ,  $-\text{SO}_2\text{-NR}^{11}\text{R}^{12}$ ,  $-\text{C(O)-R}^{10}$ ,  $-(\text{C}_0\text{-C}_4)\text{-alkyl-C(O)-O-C(R}^{15}\text{R}^{16})\text{-O-C(O)-R}^{17}$ ,  $-(\text{C}_0\text{-C}_4)\text{-alkyl-C(O)-O-C(R}^{15}\text{R}^{16})\text{-O-C(O)O-R}^{17}$ , or a residue of formula Va,





wherein  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{15}$ ,  $R^{16}$  or  $R^{17}$  are as defined above,

$R^{14}$  is halogen, methyl, ethyl or  $-NH_2$ ,

V is 1. a residue out of the group containing compounds which is derived from isoquinoline, quinoline, quinazoline, piperidine, azetidine, pyrrolidine, tetrahydropyran, piperazine and isoxazole, wherein said cyclic residue is unsubstituted or mono- or disubstituted independently of one another by  $R^{14}$ , or

2. phenyl, wherein phenyl is unsubstituted or mono- or disubstituted independently of one another by  $R^{14}$ , or

G is a direct bond,  $-(CH_2)_m-$ , or  $-(CH_2)_m-NR^{10}-$ ,

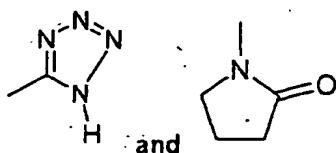
m is the integers zero, 1 or 2,

$R^{10}$  is hydrogen atom or  $-(C_1-C_4)$ -alkyl,

M is a hydrogen atom,  $(C_2-C_4)$ -alkyl, imidazolyl, pyrazolyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, or  $(C_3-C_6)$ -cycloalkyl, wherein said cyclic residues are unsubstituted or mono- or disubstituted independently of one another by  $R^{14}$

$R^{11}$  and  $R^{12}$  together with the nitrogen atom to which they are bonded can form a saturated 4- to 7-membered monocyclic heterocyclic ring which in addition to the nitrogen atom can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen out of the group azaspirodecane, azetidine, dihydrooxazole, imidazolidine, morpholine, oxazolidine, oxazepane, piperazine, piperidine, pyrazole; pyrrolidine, thiazolidine, thiomorpholine or thiophenyl, wherein said heterocyclic ring is unsubstituted or mono-, di- or trisubstituted independently of one another by  $R^{13}$ ,

$R^{13}$  is Cl,  $-CN$ ,  $=O$ ,  $-(C_0-C_2)$ -alkyl-OH,  $-(C_1-C_2)$ -alkyl,  $-(C_1-C_2)$ -alkoxy,  $-(C_3-C_6)$ -cycloalkyl,  $-(C_0-C_2)$ -alkyl- $CF_3$ ,  $-(C_0-C_2)$ -alkyl-C(O)-O- $R^{11}$ ,  $-(C_0-C_2)$ -alkyl-C(O)-N( $R^{11}$ )- $R^{12}$ ,  $-(C_0-C_2)$ -alkyl-N( $R^{11}$ )- $R^{12}$ ,  $-S(O)_2-CH_3$ ,  $-(C_0-C_2)$ -alkyl-Si( $CH_3$ )<sub>3</sub>,  $-(C_0-C_2)$ -alkyl-S(O)<sub>2</sub>-( $C_0-C_4$ )-alkyl,  $-(C_0-C_4)$ -alkyl-S(O)<sub>2</sub>-N( $R^{11}$ )- $R^{12}$ ,  $-(C_1-C_2)$ -alkylene-O-( $C_1-C_2$ )-alkyl or a residue from the following list



$R^3$  and  $R^4$  are independent of one another are identical or different and are

a) hydrogen atom,

b) F, Cl,

c)  $-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or substituted by  $R^{13}$ ,

d) phenyl, wherein phenyl is unsubstituted or substituted one to three times by  $R^{13}$ ,

e)  $-O-(C_1-C_4)$ -alkyl, wherein alkyl is unsubstituted or substituted by  $R^{13}$ ,

f)  $-C(O)-O-R^{11}$ ,

g)  $-(C_0-C_2)$ -alkyl-C(O)-N- $R^{11}R^{12}$ ,

h)  $-NR^{11}R^{12}$

i)  $-NR^{10}.SO_2-R^{10}$ ,

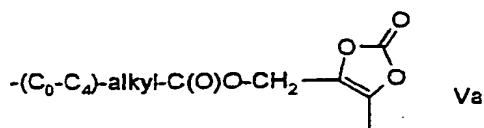
j)  $-SO_2-NR^{11}R^{12}$ ,

k)  $-C(O)-R^{10}$

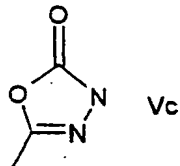
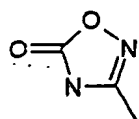
l)  $-C(O)-O-C(R^{15}R^{16})-O-C(O)-R^{17}$ , wherein  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are as defined above,

m)  $-C(O)-O-C(R^{15}R^{16})-O-C(O)O-R^{17}$ , wherein  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are as defined above,

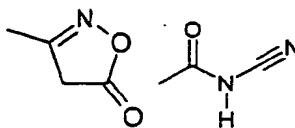
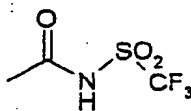
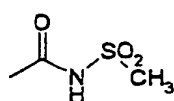
n) a residue of formula Va



10 o) a residue of formula Vb or Vc,



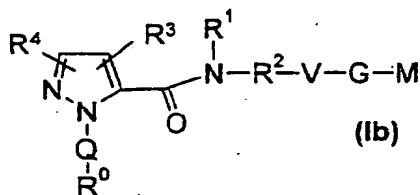
20 p) a residue from the following list



30 q) -CN or  
r) -CF<sub>3</sub>

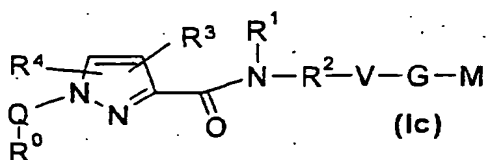
in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

6. Compound of the formula I as claimed in one or more of claims 1 to 5, wherein formula I is a compound of formula Ib



45 wherein R<sup>0</sup>; R<sup>1</sup>; R<sup>2</sup>; R<sup>3</sup>; R<sup>4</sup>; Q; V; G and M have the meanings indicated in formula I.

7. Compound of the formula I as claimed in one or more of claims 1 to 5, wherein formula I is a compound of formula Ic



wherein R<sup>0</sup>; R<sup>1</sup>; R<sup>2</sup>; R<sup>3</sup>; R<sup>4</sup>; Q; V; G and M have the meanings indicated in formula I.

8. Compound of the formula I as claimed in one or more of claims 1 to 7, wherein formula I is a compound out of the

following group

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 5 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methyl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 10 2-(6-Chloro-benzothiazol-2-yl)-5-methyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 5-(5-Chloro-thiophen-2-yl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 5-(5-Chloro-thiophen-2-yl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 15 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(2,4-dichloro-phenyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 20 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-propyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-propyl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 5-tert-Butyl-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 25 5-tert-Butyl-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-propyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 30 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-propyl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 35 2-[2-(5-Chloro-thiophen-2-yl)-thiazol-4-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[2-(5-Chloro-thiophen-2-yl)-thiazol-4-ylmethyl]-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 40 2-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-amide,  
 45 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-ylmethyl)-amide,  
 50 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-ylmethyl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-amide,  
 55 2-(4-Chloro-benzyl)-4-cyano-5-thiophen-2-yl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-(4-Chloro-benzyl)-4-cyano-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-ami-

de,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid methyl ester,

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carboxylic acid methyl ester,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid,

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carboxylic acid,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxylic acid ethyl ester,

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carboxylic acid ethyl ester,

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(morpholine-4-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(morpholine-4-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-dimethylamide 5-[(1-isopropyl-piperidin-4-yl)-amide],

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-dimethylamide 3-[(1-isopropyl-piperidin-4-yl)-amide],

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(2-hydroxy-ethyl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide],

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-amide] 3-[(1-isopropyl-piperidin-4-yl)-amide],

{[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-amino}-acetic acid,

{[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carbonyl]-amino}-acetic acid,

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(5-oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(5-oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

Sulfuric acid mono-(2-[(1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-amino)-ethyl) ester,

Sulfuric acid mono-(2-[(2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carbonyl]-amino)-ethyl) ester,

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-oxo-oxazolidine-3-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-oxo-oxazolidine-3-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-[(2-morpholin-4-yl-ethyl)-amide],

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(1-isopropyl-piperidin-4-yl)-amide] 5-[(2-morpholin-4-yl-ethyl)-amide],

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[bis-(2-methoxy-ethyl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide],

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[bis-(2-methoxy-ethyl)-amide] 3-[(1-isopropyl-piperidin-4-yl)-amide],

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(4,5-dihydro-oxazol-2-yl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide],

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(4,5-dihydro-oxazol-2-yl)-amide] 3-[(1-isopropyl-piperidin-4-yl)-amide],

2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-

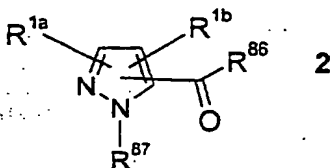
2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[3-(2-hydroxy-ethyl)-2-oxo-imidazolidine-1-carbonyl]-  
 1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-methoxymethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-  
 3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-methoxymethyl-pyrrolidine-1-carbonyl)-1H-pyrazole-  
 3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 {[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-  
 3-carbonyl]-methyl-amino}-acetic acid,  
 {[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-yl methyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-car-  
 bonyl]-methyl-amino}-acetic acid,  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-  
 3-carbonyl]-piperidine-4-carboxylic acid ethyl ester,  
 1-[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-  
 3-carbonyl]-piperidine-4-carboxylic acid ethyl ester,  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-  
 3-carbonyl]-azetidine-2-carboxylic acid,  
 1-[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-  
 3-carbonyl]-azetidine-2-carboxylic acid,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(thiomorpholine-4-carbonyl)-2H-pyrazole-3-carboxylic  
 acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(thiomorpholine-4-carbonyl)-1H-pyrazole-3-carboxylic  
 acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-  
 3-carbonyl]-pyrrolidine-2-carboxylic acid,  
 1-[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-  
 3-carbonyl]-pyrrolidine-2-carboxylic acid,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4-hydroxy-piperidine-1-carbonyl)-2H-pyrazole-3-car-  
 boxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4-hydroxy-piperidine-1-carbonyl)-1H-pyrazole-3-car-  
 boxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-  
 3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-1H-pyrazole-  
 3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-pyrrolidine-1-carbonyl)-2H-pyrazole-3-car-  
 boxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-pyrrolidine-1-carbonyl)-1H-pyrazole-3-car-  
 boxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 5-(2,5-Bis-methoxymethyl-pyrrolidine-1-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-  
 pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 5-(2,5-Bis-methoxymethyl-pyrrolidine-1-carbonyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-  
 pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4-hydroxymethyl-piperidine-1-carbonyl)-2H-pyrazole-  
 3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4-hydroxymethyl-piperidine-1-carbonyl)-1H-pyrazole-  
 3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 5-(8-Aza-spiro[4.5]decane-8-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-car-  
 boxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 5-(8-Aza-spiro[4.5]decane-8-carbonyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3-car-  
 boxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-methanesulfonyl-pyrrolidine-1-carbonyl)-2H-pyra-  
 zole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-methanesulfonyl-pyrrolidine-1-carbonyl)-1H-pyra-  
 zole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(1,1-dioxo-tetrahy-  
 dro-1-thiophen-3-yl)-methyl-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide],  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1,1-dioxo-tetrahy-

dro-1-thiophen-3-yl)-methyl-amide] 3-[(1-isopropyl-piperidin-4-yl)-amide],  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-azetidine-3-carboxylic acid,  
 1-[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carbonyl]-azetidine-3-carboxylic acid,  
 5 (Azetidine-1-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 5-(Azetidine-1-carbonyl)-1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-oxo-piperazine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-oxo-piperazine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4,4-difluoro-piperidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4,4-difluoro-piperidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[(1,4)oxazepane-4-carbonyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[(1,4)oxazepane-4-carbonyl]-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-trifluoromethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-trifluoromethyl-pyrrolidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2,2-dimethyl-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2,2-dimethyl-pyrrolidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-[(2-sulfamoyl-ethyl)-amide],  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(1-isopropyl-piperidin-4-yl)-amide] 5-[(2-sulfamoyl-ethyl)-amide],  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-cyclopropylamide 5-[(1-isopropyl-piperidin-4-yl)-amide],  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-cyclopropylamide 3-[(1-isopropyl-piperidin-4-yl)-amide],  
 {[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-amino}-methanesulfonic acid,  
 {[2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-2H-pyrazole-3-carbonyl]-amino}-methanesulfonic acid,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-cyclobutylamide 5-[(1-isopropyl-piperidin-4-yl)-amide],  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-cyclobutylamide 3-[(1-isopropyl-piperidin-4-yl)-amide],  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperidin-4-yl)-amide] 3-[(2-methoxy-ethyl)-amide]  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(1-isopropyl-piperidin-4-yl)-amide] 5-[(2-methoxy-ethyl)-amide],  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(pyrrolidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(pyrrolidine-1-carbonyl)-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(cyanamide-1-carbonyl)-2H-pyrazole-3-carboxylic acid

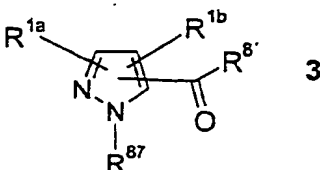
(1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(cyanamide-1-carbonyl)-1H-pyrazole-3-carboxylic acid  
 (1-isopropyl-piperidin-4-yl)-amide,  
 Phosphoric acid mono-(2-[[1-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-yl-  
 5 carbamoyl)-1H-pyrazole-3-carbonyl]-amino]-ethyl) ester,  
 Phosphoric acid mono-(2-[[2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-yl-  
 carbamoyl)-2H-pyrazole-3-carbonyl]-amino]-ethyl) ester,  
 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxyl-  
 ic acid methyl ester,  
 10 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carboxyl-  
 ic acid,  
 1-[(5-Chloro-pyridin-2-ylcarbamoyl)-methyl]-1H-pyrazole-3,5-dicarboxylic acid 3-cyclobutylamide 5-[(1-isopro-  
 pyl-piperidin-4-yl)-amide],  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1-isopro-  
 15 pyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid bis-[(1-isopropyl-piperi-  
 din-4-yl)-amide],  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperi-  
 din-4-yl)-amide,  
 20 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-cyano-1H-pyrazole-3-carboxylic acid (1-isopropyl-piperi-  
 din-4-yl)-amide,  
 2-[(4-Chloro-phenylcarbamoyl)-methyl]-4-cyano-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-  
 amide,  
 3-[[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-  
 25 3-carbonyl]-amino]-propionic acid,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperid-  
 in-4-yl)-amide] 3-(methoxy-amide),  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-carbamoylmethyl-amide  
 5-[(1-isopropyl-piperidin-4-yl)-amide],  
 30 {[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-yl methyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-  
 carbonyl]-amino}-acetic acid ethyl ester,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(3-hydroxy-propyl)-  
 amide] 5-[(1-isopropyl-piperidin-4-yl)-amide],  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-  
 35 3-carbonyl]-(2S)-azetidine-2-carboxylic acid,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2S,2-hydroxymethyl-pyrrolidine-1-carbonyl)-2H-pyra-  
 zole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-  
 carbonyl]-2S-pyrrolidine-2-carboxylic acid,  
 40 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2S,2-methoxymethyl-pyrrolidine-1-carbonyl)-2H-pyra-  
 zole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 5-(2R,5R,2,5-Bis-methoxymethyl-pyrrolidine-1-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-  
 2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(4,5-dihydro-oxazol-  
 45 2-yl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide],  
 1-[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-  
 carbonyl]-piperidine-4-carboxylic acid ethyl ester,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperid-  
 in-4-yl)-amide] 3-[(2-morpholin-4-yl-ethyl)-amide],  
 50 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(4,4-difluoro-piperidine-1-carbonyl)-2H-pyrazole-3-car-  
 boxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(2-oxo-oxazolidine-3-carbonyl)-2H-pyrazole-3-carboxyl-  
 ic acid (1-isopropyl-piperidin-4-yl)-amide,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperid-  
 in-4-yl)-amide] 3-[[2-(2-oxo-imidazolidin-1-yl)-ethyl]-amide],  
 55 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5-[(1-isopropyl-piperid-  
 in-4-yl)-amide] 3-[(2,2,2-trifluoro-ethyl)-amide],  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 3-[(1,1-dioxo-tetrahy-

dro-1-thiophen-3-yl)-amide] 5-[(1-isopropyl-piperidin-4-yl)-amide],  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1-isopropyl-piperidin-4-yl)-amide] 3-[[3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide],  
 5-(Azetidine-1-carbonyl)-2-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(thiazolidine-3-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[[1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(1-isopropyl-piperidin-4-ylcarbamoyl)-1H-pyrazole-3-carbonyl]-amino]-3,3,3-trifluoro-propionic acid,  
 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1H-pyrazole-3,5-dicarboxylic acid 5- [(1-isopropyl-piperidin-4-yl)-amide] 3-trimethylsilanylmethyl-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-[4-(2-oxo-pyrrolidin-1-yl)-piperidine-1-carbonyl]-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide,  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-methanesulfonylaminocarbonyl-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide and  
 2-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(3-hydroxy-azetidine-1-carbonyl)-2H-pyrazole-3-carboxylic acid (1-isopropyl-piperidin-4-yl)-amide.

9. A process for the preparation of a compound of the formula I as claimed in one or more of claims 1 to 8, which comprises condensing a corresponding carboxylic acid of the formula 2



with a compound of the formula  $\text{HR}^{8'}$  or with an amine of the formula  $\text{HN}(\text{R}^1)\text{R}^2\text{-V-G-M}$  to give a compound of the formula 3



and optionally converting the compound of formula 3 into a compound of the formula I, wherein the groups  $\text{R}^{8'}$  and  $\text{R}^{87}$  are the groups  $\text{-N}(\text{R}^1)\text{-R}^2\text{-V-G-M}$  and  $\text{R}^0\text{-Q-}$  and are as defined in the formula I and  $\text{R}^{1a}$  and  $\text{R}^{1b}$  have the meaning of  $\text{R}^3$  and  $\text{R}^4$  in formula I.

10. A pharmaceutical preparation, comprising at least one compound of the formula I as claimed in one or more of claims 1 to 8 in all its stereoisomeric forms and mixtures thereof in any ratio and/or its physiologically tolerable salts and a pharmaceutically acceptable carrier.
11. The use of a compound of the formula I as claimed in one or more of claims 1 to 8 in all its stereoisomeric forms and mixtures thereof in any ratio and/or their physiologically tolerable salts for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis.
12. The use as claimed in claim 11 for influencing blood coagulation, inflammatory response, fibrinolysis, cardiovascular disorders, thromboembolic diseases, restenoses, abnormal thrombus formation, acute myocardial infarction, unstable angina, acute vessel closure associated with thrombolytic therapy, thromboembolism, percutaneous, pathologic thrombus formation occurring in the veins of the lower extremities following abdominal, knee and hip surgery, transluminal coronary angioplasty, transient ischemic attacks, stroke, disseminated systemic intravascular



# EP 1 433 788 A1

coagulopathy occurring in vascular systems during septic shock, a risk of pulmonary thromboembolism, certain viral infections or cancer, intravascular coagulopathy occurring in vascular systems during septic shock, coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure, stroke and disseminated intravascular clotting disorder, thromboses like deep vein and proximal vein thrombosis which can occur following surgery.

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European Patent  
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# PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 02 02 8915

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 2002/091116 A1 (JIA ZHAOZHONG JON ET AL) 11 July 2002 (2002-07-11) * claims; examples 9,10,22,46-49 *	1-7,9-12	C07D413/14 A61K31/4155 A61K31/42 A61K31/4535
X	WO 02 085356 A (SQUIBB BRISTOL MYERS CO) 31 October 2002 (2002-10-31) * claims 1,7; examples 1,9 *	1-7,9-12	A61P7/02 C07D417/14 C07D409/14 C07D401/14 C07D213/61
X	WO 01 19798 A (COR THERAPEUTICS INC) 22 March 2001 (2001-03-22) * claims 8,9,12,13,15,19; examples 9-13,22,28,45,47 *	1-7,9-12	
X	US 6 339 099 B1 (LAM PATRICK Y ET AL) 15 January 2002 (2002-01-15) * examples 104,114-117; table 2 *	1-7,9-12	
X	WO 99 32454 A (DU PONT PHARM CO) 1 July 1999 (1999-07-01) * table 2 *	1-7,9-12	
X	US 6 020 357 A (ORWAT MICHAEL JAMES ET AL) 1 February 2000 (2000-02-01) * table 2 *	1-7,9-12	
-/-			TECHNICAL FIELDS SEARCHED (Int.Cl.7) C07D A61K A61P
INCOMPLETE SEARCH			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely:</p> <p>Claims searched incompletely:</p> <p>Claims not searched:</p> <p>Reason for the limitation of the search: see sheet C</p>			
Place of search THE HAGUE		Date of completion of the search 29 September 2003	Examiner De Jong, B
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>	
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>			

EPO FORM 1503 03.02 (P04C07)



European Patent  
Office

INCOMPLETE SEARCH  
SHEET C

Application Number  
EP 02 02 8915

Claim(s) searched completely:  
8,11,12

Claim(s) searched incompletely:  
1-7,9-10 (all in part)

Reason for the limitation of the search:

The initial phase of the search, even when restricted to compounds according to the first and fourth invention, revealed a large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 84 EPC). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search was only complete for compounds according to claim 8.

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.CL7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	WO 01 29006 A (DU PONT PHARM CO) 26 April 2001 (2001-04-26) * claim 13 *	1-7,9-12	
X	WO 01 32628 A (DU PONT PHARM CO ;PINTO DONALD J P (US)) 10 May 2001 (2001-05-10) * claim 1; examples *	1,9-12	
X	WO 98 28269 A (DU PONT MERCK PHARMA) 2 July 1998 (1998-07-02) * claims *	1,10-12	
X	EP 0 477 049 A (SANOFI SA) 25 March 1992 (1992-03-25) * claim 1 *	1	TECHNICAL FIELDS SEARCHED (Int.CL7)
X	WO 00 69849 A (ORTHO MCNEIL PHARM INC) 23 November 2000 (2000-11-23) * claims; examples 114-117 *	1	



European Patent  
Office

Application Number

EP 02 02 8915

### CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

### LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- ☒ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:  
1-12 (in part: inventions 1 and 4))
- ☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

European Patent  
OfficeLACK OF UNITY OF INVENTION  
SHEET BApplication Number  
EP 02 02 8915

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

## 1. Claims: 1-12 (in part)

Compounds of formula (I) in which R<sub>0</sub> is a monocyclic or bicyclic 6- to 14-membered aryl substituted by at least one R<sub>8</sub> which is halogen.

## 2. Claims: 1-7,9-12 (all in part)

Compounds of formula (I) in which R<sub>0</sub> is a monocyclic or bicyclic 6- to 14-membered aryl substituted by at least one R<sub>8</sub> which is -C(=O)-NH<sub>2</sub>.

## 3. Claims: 1-7,9-12 (all in part)

Compounds of formula (I) in which R<sub>0</sub> is a monocyclic or bicyclic 6- to 14-membered aryl substituted by at least one R<sub>8</sub> which is -O-(C<sub>1</sub>-C<sub>8</sub>)-alkyl.

## 4. Claims: 1-12 (in part)

Compounds of formula (I) in which R<sub>0</sub> is pyridyl or phenylpyridyl.

## 5. Claims: 1-12 (in part)

Compounds of formula (I) in which R<sub>0</sub> is pyrimidyl.

## 6. Claims: 1-12 (in part)

Compounds of formula (I) in which R<sub>0</sub> is indolyl or isoindolyl.

## 7. Claims: 1-12 (in part)

Compounds of formula (I) in which R<sub>0</sub> is indazolyl or phthalazinyl.

## 8. Claims: 1-12 (in part)

Compounds of formula (I) in which R<sub>0</sub> is quinolyl or isoquinolyl.

## 9. Claims: 1-12 (in part)



European Patent  
Office

LACK OF UNITY OF INVENTION  
SHEET B

Application Number

EP 02 02 8915

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Compounds of formula (I) in which R0 is benzothiazolyl

10. Claims: 1-12 (in part)

Compounds of formula (I) in which R0 is benzothiophene

11. Claims: 1-12 (in part)

Compounds of formula (I) in which R0 is quinazoliny1

12. Claims: 1-12 (in part)

Compounds of formula (I) in which R0 is a monocyclic or bicyclic 4- to 15-membered heteroaryl additionally substituted by a monocyclic or bicyclic 4- to 15-membered heteroaryl

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 02 02 8915

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

29-09-2003

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